SULFA RESIDUES IN PORK: AN UPDATE

John K. Augsburg

Food and Drug Administration
Rockville, MD 20857

ABSTRACT

Sulfamethazine (SMZ) is an antibacterial drug used in approximately 75% of all hogs marketed in the U.S. The tolerance for residues of SMZ in uncooked tissues is .1 ppm, and the withdrawal time is 15 d. The rate of illegal residues in swine from the use of SMZ has continued to fluctuate between 4% and 5% from 1980 through 1987. This was not acceptable. The Center for Veterinary Medicine (CVM) also has received from the National Center for Toxicological Research a report showing that SMZ produces a dose-related increase in follicular cell adenomas of the thyroid gland in rats and mice. The FDA has discovered three major causes of SMZ residues by investigating violators. The number one cause was a lack of sequencing, flushing, and cleaning of mixer equipment. Failure to follow withdrawal times was another major cause, and the third major reason was the use of a soluble powder solution. At least 16% of SMZ residue violations have resulted in no follow-up due to lack of animal identification. The FDA district offices are conducting on-farm investigations of swine producers who have caused SMZ violations. Repeat violators and those that produce higher residue levels will receive a higher priority. The FDA currently is attempting to obtain more state support, particularly for investigation of first-time violators. The CVM is serious about resolving the SMZ residue problem. (Key Words: Sulfonamides, Residues, Pork.)

Introduction

Sulfamethazine is an antibacterial drug widely used in food-producing animals, particularly in swine and cattle. The tolerance for residues of sulfamethazine in uncooked tissues is .1 ppm. The withdrawal time is 15 d. In 1987 about 75% of all hogs marketed in the U.S. received some sulfa medication, with sulfamethazine the leading drug of choice. In swine production, sulfonamides are used to treat bacterial pneumonia, atrophic rhinitis and bacterial enteritis. They also are used for improving efficiency of feed utilization and for growth promotion.

Background

The FDA has been concerned for over a decade about the high violation rate in swine from the use of sulfamethazine. Efforts of the USDA and FDA to reduce the violation rate have helped but have never been able to bring the rate down to an acceptable level. The annual violative rate was around 13% of swine tested prior to 1978. In 1978 extensive training and educational programs were instituted by the USDA and FDA under the Residue Avoidance Program. At about this time the drug manufacturing industry contributed to these efforts by developing a granular form of sulfamethazine. Also, the withdrawal time was increased from 7 d to the present 15 d. Although these programs noticeably reduced the rate of illegal residues, the violation rate has continued to fluctuate between 4 and 5%.

Although the national average for 1987 was slightly above 4%, data from individual states showed much higher violation rates, especially...
in some of the major swine producing states. However, the higher state results are unofficial and no confirmations were run after the SOS (Sulfa-on-Site) tests. The SOS test is an in-plant rapid screening test using urine samples and can be used either pre-slaughter or post-slaughter. The test also will be used to indicate to producers that a group of live hogs is free of violative residues. In addition to our concern for these high violative residue rates, the Center for Veterinary Medicine (CVM) has received the results from the National Center for Toxicological Research (NCTR) of a chronic toxicity study (National Center for Toxicological Research, 1988a). The report has shown that sulfamethazine produces a dose-related increase in follicular cell adenomas of the thyroid gland in both male and female mice. This increase was noted after feeding moderate-to-high doses of sulfamethazine for 18 and 24 mo\(^3\). We also have received the results from NCTR of a chronic study in rats that has just been completed (National Center for Toxicological Research, 1988b). These reports currently are under peer review in CVM. In addition, NCTR's tissue slides will be reviewed by an outside pathology group under the aegis of the National Program.

The Center, besides reviewing the NCTR reports, also has begun a causal review of the safety data associated with the New Animal Drug Application (NADA) approvals for all sulfamethazine products. Letters were sent to the 43 holders of approved NADA requesting submission of any data not previously submitted to the agency regarding the safety of the drug.

The CVM also is in the process of drafting a revocation notice for the removal from the market of products associated with 21 CFR 510.450. Many of these 143 NADA are sulfamethazine-containing products that have enjoyed interim marketing prior to being approved since the early 1970s. The sponsors of these, of which there are 11, have been notified on numerous occasions that the data submitted with these NADA were insufficient for approval. In addition to the revocation notice, the Center is preparing a Notice of Opportunity for Hearing on a refusal to approve these NADA.

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\(^3\)Sulfamethazine in the diet was at dose levels of 0, 300, 600, 1,200, 2,400 and 4,800 ppm.

Residue Testing: Phase I

On March 7, 1988, the FSIS initiated Phase I of an intensified inspection program, testing the muscle tissue of swine for sulfamethazine residues. Two samples per week were obtained from 100 slaughter establishments. These plants slaughter approximately 96% of the market hogs and are located in 30 states. This completed program sampled over 1,600 tissues and found 30 violations (1.9%). The largest number of violations (8 and 7) were found in the Atlanta and Nashville FDA districts, respectively. This includes Georgia, Alabama, Mississippi, Kentucky, Tennessee, and the Carolinas.

The residue violations in the Phase I testing of muscle tissue ranged from .12 to 2.34 ppm. A breakdown revealed that 57% of these violations were between .1 ppm and .3 ppm and 21% were between .4 ppm and .6 ppm. Six violations were over 1.0 ppm. On an individual basis, three of these six received medicated feed up until the time of slaughter. One involved a producer using medicated feed containing SMZ who had not flushed the mixing equipment. This producer's trailer used to transport the hogs to market also was contaminated. Another incident involved a producer using powdered SMZ, and cross-contamination of finishing feeds therefore was possible. The final violation involved a farmer who gave his hogs a liquid SMZ medication prepared by a veterinarian for use on a sick cow.

The FDA has discovered three major causes of SMZ residues in these 30 Phase I follow-up visits to violators. A lack of sequencing, flushing, and cleaning of mixer equipment accounted for about 25% of violations. Failure to follow withdrawal time was another major cause. The third major reason was the use of a soluble powder solution. Numerous miscellaneous causes also were found, ranging from an employee feeding error to SMZ-contaminated pond water being recycled for flushing pens.

It is noteworthy that a lack of animal identification presented a problem in 7 of the 30 reported violations. This continues to hinder FDA follow-up investigations and should be corrected when the swine identification proposal is implemented. The Animal Plant Health Inspection Service (APHIS) of USDA has the lead in this project, and they are nearing completion of their review on all
responses received following the proposal publication in February (USDA, 1988).

**Residue Testing: Phase II**

The FSIS began Phase II of their intensified program on April 4, 1988. Phase II involves the rapid in-plant Sulfa-on-Site (SOS) testing of swine urine (FSIS, 1987). This has been implemented gradually and, as of now, all 100 slaughter establishments are currently on-line.

As of July 15, 1988, the CVM had received 115 violative Phase II sample reports out of 21,361 swine tested (.54%). These have been confirmed using muscle tissue. The major causes for residue violations paralleled those of Phase I, with cross-contamination of mixing equipment and failure to follow proper withdrawal times being the most prevalent causes.

At least 11 additional violations in Phase II have resulted in closed cases due to the fact that producer identification could not be established. Therefore, a total of 18 of 116 residues, 16%, have resulted in no follow-up due to the problem of identification. An effective identification system to trace animals from production unit through the marketing and processing chain is absolutely essential to identifying the cause of violative residues and the responsible party or parties.

The largest number of residues has occurred in the Atlanta, Kansas City, and Nashville districts. Over 50% of the total reported in both Phase I and II have come from those three districts. States in the Kansas City district include Missouri, Kansas, Iowa and Nebraska.

**Proper Use of Sulfamethazine**

The CVM frequently is asked if the number of sulfamethazine residue violations is as large as anticipated. The answer is clearly no. The next question is, Why not? We see several possible reasons. The use of the drug in the swine industry has been reduced. The National Pork Producers Council (NPPC) recently has completed a survey showing a 30% to 50% reduction in the use of SMZ among swine producers they polled. In the feed industry, some manufacturers have suspended the sale of products containing sulfamethazine.

Many producers and feed manufacturers who continue to use the drug are doing so with greater concern. Very strict quality control programs are being followed, increased testing of feeds is being conducted, and strict SMZ inventory control procedures have been implemented by the feed industry.

Educational programs on the proper use of sulfamethazine have been developed and presented to swine producers. This is an important aspect, because about 70% of all swine finishing feeds are mixed on the farm.

Studies on the use of sulfamethazine in swine have been carried out in several states. An Indiana project conducted by Purdue University in conjunction with 80 Indiana farmers concluded that the following contributed to increased risk of cross-contamination of feed (Powell et al., 1984): 1) use of powdered rather than granular sulfamethazine, 2) higher than approved levels of sulfamethazine in use, 3) high volume of medicated feed mixed on the farm and 4) inadequate feed sequencing and equipment flushing and cleaning methods.

An Illinois project confirmed many of the Indiana findings (Biehl, 1984). In Iowa, more than one-third of the finishing feed samples collected in one study were contaminated at a level sufficient to cause a violative residue. Studies in Kentucky suggest that failure to expel medicated feed from grinding/mixing equipment before preparing unmedicated feed is the most frequent cause of sulfa residues. Most of these factors were within the control of the farmer alone, with little veterinary involvement documented.

Ideally, each pork producer should establish a drug use program with his/her veterinarian. On-farm monitoring could include testing swine urine, feed, and perhaps water. Complete feed preparation records are very important.

One thing to keep in mind is that many sulfa residues are caused by either cross-contamination of withdrawal feed or failure to follow the proper withdrawal time, sometimes unknowingly. Only a small amount of sulfamethazine is required to cause a violation. As little as 1 ppm in the feed is enough to cause a violative residue. Ten kilograms of a sulfamedicated feed carried over into the following 1,000 kg of feed can cause the next batch to contain enough sulfa to potentially cause a violation.

The following procedures should help avoid cross-contamination. First, use a sequencing pattern. Mix a batch of feed to be fed to hogs...
not going to market between the mixing of a sulfa-medicated ration and the withdrawal feed. Second, flush the mixing and delivery system after a sulfa feed has been mixed. Use this flush material for hogs not going to market. Third, clean equipment after sulfa feed is mixed or transported.

There are other important farm management practices that should be followed. It is imperative to follow established withdrawal times. The proper dosage should be used and sulfamethazine should not be used at higher than label-recommended doses. No powdered SMZ should be mixed in the feed. For the withdrawal period, feeders should be used that are never used for sulfa-medicated feed. It also is important to prevent manure buildup in the pens, which would allow recycling of sulfa.

**FDA Public Hearing**

A public hearing before the Commissioner of Food and Drugs was held May 25 and 26, 1988 to provide an opportunity for interested persons to present relevant scientific data on the safety of SMZ, and on whether it can be used in food-producing animals without the occurrence of residues in tissue or milk (FDA, 1988a).

The hearing involved approximately 8 h of testimony from 22 representatives, and additional written information could be submitted before June 27. In fact, the Commissioner asked for specific information from a number of the participants.

Dr. Frank Young, Commissioner of Food and Drugs, concluded the May hearing by presenting the three options he perceived. The first option is recommending that the Secretary of HHS find that sulfamethazine presents an imminent hazard to the public health and suspend approval of the sulfamethazine NADA. This would provide an immediate ban. The second is issuing a notice of opportunity of hearing proposing to withdraw approval of the NADA for SMZ for use in food animals. This option would take much longer than an imminent hazard. The third possibility is developing a comprehensive voluntary program to substantially reduce the incidence of illegal residues. This would involve extensive testing, monitoring and enforcement. It also may involve the lowering of the tolerance level.

**FDA On-Farm Investigations**

In the meantime, FDA district offices will conduct follow-up, on-site, on-farm investigations of swine producers to determine the cause of SMZ violations (FDA, 1988b). The purpose of these inspections will be to prevent a repeat SMZ tissue residue violation through an FDA presence, to provide education, and to issue a regulatory letter or initiate legal action when warranted. FDA districts will prioritize their investigations as follows: 1) repeat violators will be of higher priority than initial violators; 2) the higher the residue level, the higher the priority; 3) large producers with frequent shipments of animals will be followed up before small producers shipping few animals; and 4) producers shipping large numbers of animals interstate will be given a higher priority than producers shipping entirely or primarily intrastate.

The districts will be unable to conduct a follow-up investigation for SMZ violative residues under the following circumstances: 1) no producer or other responsible party is identified by FSIS; 2) the violator identified by FSIS is found not to be the producer or responsible party, and, due to lack of animal identification, the producer or responsible party cannot readily be determined; or 3) the SOS test results were positive, but were not confirmed by laboratory analysis.

Currently, the Division of Federal-State Relations is working to arrange for states to conduct on-farm investigations for the FDA, especially for first-time violators. Districts will not conduct follow-up investigation for SMZ violative residues when a state agency is involved.

The FDA is seeking increased cooperative support in this program area. Under a Memorandum of Understanding (MOU) with the FDA and FSIS, the states of Delaware, Maryland, Pennsylvania, Virginia and West Virginia already participate in successful cooperative tissue residue programs with no funding involved. There is an ongoing effort to interest other states, and the SMZ residue problem provides an opportune circumstance to expand this cooperation. In the long term, state participation should improve the FDA's resource picture and greatly improve consumer protection.

The FDA will not have sufficient resources to accomplish these investigations alone. A
combined federal-state-industry approach is needed. The FDA has been successful in obtaining the assistance of several states to participate in follow-up of first-time residue violators. In addition, states have offered assistance in the producer identification process.

Some funds may be available for funding up to 10 states interested in the SMZ residue program. Anyone desiring more specific information may call CVM's Tissue Residue Branch or contact their FDA district office. States will be given the opportunity to submit proposals when all of the details of this program are in place.

In summary, there are three separate approaches for FDA-FSIS-state cooperative work efforts in the residue area. One is under a Memorandum of Understanding (MOU). A second is through an informal agreement. The third is in the area of funding states through a contract arrangement.

Summary

The CVM has been encouraged by the fact that pork producers, food animal veterinarians, the animal health industry and other groups recognize SMZ residues as a serious problem. The CVM is serious about resolving this problem. We must have an effective identification program to locate the few flagrant violators who are responsible for residues over 1.0 ppm. They must be held accountable for their actions. This group must be penalized and these actions must be publicized. We must detect, identify, find the cause, and initiate corrective actions for all SMZ violative residues. Let's continue our record of providing one of the safest, healthiest and most economical food supplies in the world. The CVM is interested in working with all segments of the industry and is ready to move ahead as rapidly and as effectively as possible on this issue.

Literature Cited


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