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Report to the Chairman, Human Resources and Intergovernmental Relations Subcommittee, Committee on Government Operations, House of Representatives

August 1992

FOOD SAFETY AND QUALITY

FDA Strategy Needed to Address Animal Drug Residues in Milk

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Resources, Community, and
Economic Development Division

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The Honorable Ted Weiss
Chairman, Human Resources and
Intergovernmental Relations
Subcommittee
Committee on Government Operations
House of Representatives

Dear Mr. Chairman:

This report responds to your request that we review (1) the Food and Drug Administration's (FDA) and the states' efforts to test for and control animal drug residues in milk and (2) FDA's extra-label drug use policy, under which FDA generally will not pursue enforcement action when veterinarians violate the law by treating a food animal, under emergency circumstances, with drugs not in accordance with approved drug labels. This report makes recommendations for improving milk monitoring to the Commissioner, FDA.

Copies of this report will be sent to the Secretary of Health and Human Services; the Commissioner, FDA; and interested congressional committees. We will also make copies available upon request.

This review was conducted under the direction of John W. Harman, Director, Food and Agriculture Issues, who may be reached at (202) 275-5138. Other major contributors to this report are listed in appendix III.

Sincerely yours,

J. Dexter Peach
Assistant Comptroller General

Executive Summary

Purpose

The Food and Drug Administration (FDA), together with the states and the dairy industry, oversees the safety and purity of the nation's milk supply. Over the last several years, a number of federal and private reports, including GAO's, have raised questions about the amount of animal drug residues in milk. Concerned about milk safety, the Chairman, Human Resources and Intergovernmental Relations Subcommittee, House Committee on Government Operations, asked GAO to review federal and state efforts to test for and control animal drug residues in milk.

Background

FDA is responsible, under the Federal Food, Drug, and Cosmetic Act (FFDCA), for ensuring that milk products are safe. Under a cooperative federal/state agreement and the Pasteurized Milk Ordinance, FDA oversees state regulators who perform day-to-day oversight of the milk supply, including monitoring for residues.

Animal drugs used to treat dairy cows may leave residues in milk. FDA is also responsible for determining whether animal drugs are safe and effective and for setting legal limits on the residues that may remain in food products. Use of an animal drug on a dairy cow other than as specified on the FDA-approved label (called extra-label use) is illegal and may cause unsafe residues in milk that may be a health hazard to consumers. However, under FDA's 1984 extra-label use policy, FDA generally will not pursue enforcement action when veterinarians treat a food animal with a drug or dosage level not approved for the animal if the animal's life is in danger and no other effective approved drugs are available.

Results in Brief

A large gap exists between the number of drugs used to treat dairy cows and the number of drugs FDA and states test for in milk. States are routinely testing, under the Milk Ordinance, for only 4 drugs, while up to 82 drugs that may leave residues in milk may be in use. In 1991 FDA estimated on the basis of state tests that up to 1 percent of the milk produced was contaminated with excess residues of these four drugs and was discarded. The amount of additional milk that may be contaminated by other drugs that are not tested for is unknown. Over half of the drugs that may be used on dairy cows are not approved for use in dairy cows, and some are not approved for any food-producing animal.

Although FDA intended that extra-label drug uses by veterinarians would occur in rare or emergency circumstances, such use is in fact routine.

Because FDA has not reviewed extra-label uses, important safety data and a test method to detect possible residues in milk are usually not available. As a result, extra-label uses could cause potentially unsafe residues in milk that escape detection. Furthermore, dairy farmers can purchase most animal drugs over the counter, creating the potential for their misuse.

Recognizing the gap between drug usage and testing, in April 1991 FDA, the states, and industry revised the Milk Ordinance. The revisions require FDA to identify additional drugs to test for and recommend additional test methods for the states and industry to use. However, as of July 1992 FDA had not completed either of these efforts and did not have a comprehensive strategy for accomplishing the needed changes.

Principal Findings

Gap Between Animal Drug Usage and Testing Is Substantial

Since 1980 the states have routinely tested milk for only 4 of the 82 animal drugs that may be used on dairy cows and could leave residues in milk. On the basis of tests for these four drugs in 1991, FDA estimated that up to 1 percent of the nation's milk supply was contaminated with excess animal drug residues and had been discarded. Although some states and parts of the milk industry are now supplementing required tests with screening tests, there are no reliable data on the number or type of tests done, or the test results. Consequently, the actual extent of contamination is probably greater because many of the drugs that are not routinely tested for are widely used. For example, FDA data indicate that 64 of the drugs are commonly used on dairy cows or may leave residues that raise health concerns. Moreover, 35 of these 64 drugs are not approved for use on dairy cows, and still others are not approved for use in any food animals.

Extra-Label Drug Use Is Routine

Use of an animal drug other than specified on the FDA-approved label is a violation of FFDCA. However, under FDA's extra-label use policy, a veterinarian can use an approved animal drug in an unapproved manner to treat dairy cows under emergency circumstances. For example, a veterinarian could use a drug approved for use only on horses to treat dairy cows. Although FDA intended that extra-label uses under its policy would be rare, several veterinarians who treat dairy cows told GAO that 40 to 85 percent of their dairy cow prescriptions are for extra-label uses.

Veterinarians and FDA officials contend that extra-label use is necessary because there are not enough approved drugs to effectively treat all dairy cow diseases. However, FDA lacks data from a scientific source, such as the National Academy of Sciences, on the need for extra-label uses and on whether veterinarians have sufficient information to make informed decisions about extra-label uses. FDA also lacks data on whether, or to what degree, veterinarians are adhering to the conditions of the policy. Proposals to revise FDA's policy, or to legalize extra-label uses, are limited by the same lack of data.

In addition to extra-label uses of animal drugs by veterinarians, dairy farmers have access to a range of animal drugs through both veterinarian prescriptions and over-the-counter sales. For example, FDA inspection data from 1990 and 1991 indicated that 62 animal drugs not approved for use on dairy cows were found on dairy farms across the nation; 42 drugs were not approved for use in any food-producing animal. An FDA official told GAO that use of these drugs by dairy farmers is extensive, but reliable information on the extent of such use does not exist.

Limited Progress in Implementing Program Revisions

The Milk Ordinance was revised in April 1991 to expand state and industry testing of milk by using additional tests to check for residues not currently monitored. However, state monitoring required by the Milk Ordinance has not been expanded beyond the four drugs because FDA has not met scheduled deadlines for recommending additional tests. FDA and the AOAC Research Institute, a standard-setting organization, were to develop a program to evaluate new tests by July 1992, but the Institute now estimates that it will be fall 1992 before it can begin evaluating tests. As a result, additional methods will not be available until 1993 at the earliest.

In 1991 FDA began its own program to monitor residues of 12 drugs in milk. However, the program's small sample size and the limited number of drugs tested for preclude drawing any statistically valid conclusions about the presence of residues in milk. This raises questions about the value of this program and how it fits into the overall milk monitoring effort.

FDA is also developing test methods to identify and measure the residues of 48 animal drugs in milk. However, these methods require specialized laboratory equipment and are time-consuming to run. State and industry officials told GAO that FDA's methods are not suitable for and not responsive to their needs for quick, reliable, inexpensive screening tests that can be used in the field to check raw milk before processing.

Frustrated by FDA delays, some states and parts of the industry have started using screening tests on their own. However, these tests have not been completely validated and are not being consistently used.

Overall, FDA lacks a comprehensive strategy for monitoring animal drugs in milk that optimizes state and industry monitoring under the Milk Ordinance; integrates federal, state, and industry testing efforts; and outlines roles and responsibilities. Lacking clear federal leadership, some states and parts of the industry have taken actions on their own. While commendable, these efforts do not represent a comprehensive, uniform, or required system that will provide consumers with assurance that the milk supply is free of excess animal drug residues.

Recommendations

To better ensure the safety of the nation's milk supply, GAO recommends that the Commissioner, FDA, develop a comprehensive strategy to monitor milk for animal drugs that optimizes state and industry monitoring under the Milk Ordinance, outlines FDA offices' roles and responsibilities, and integrates the various efforts to improve milk monitoring. FDA's strategy should, at a minimum, (1) develop an action plan to implement the 1991 revisions to the Milk Ordinance, focusing on those drugs that pose the greatest threat to consumer safety, (2) resolve which types of test methods are necessary for the states and industry to use under the Milk Ordinance, and (3) reexamine the objectives and mission of FDA's monitoring program to determine its relationship to state and industry testing under the Milk Ordinance. GAO is also recommending other actions that FDA should take in conjunction with, or as interim measures pending completion of, the comprehensive strategy, including further restricting the extra-label use of animal drugs on dairy cows.

Agency Comments

As requested, GAO did not obtain written agency comments on a draft of this report. GAO did, however, discuss the factual content of the report with FDA, state, and industry officials, who generally agreed with its accuracy. These groups believed that substantial progress has been made in monitoring milk for residues in the past few years, including revising the Milk Ordinance. However, they also expressed frustration at the slow progress in other areas—for example, the lack of enough approved drugs for dairy cows or additional screening tests. Where appropriate, GAO made revisions on the basis of these discussions.

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Abbreviations

AHI	Animal Health Institute
AVMA	American Veterinary Medical Association
CFSAN	Center for Food Safety and Applied Nutrition, FDA
CVM	Center for Veterinary Medicine, FDA
FDA	Food and Drug Administration
FFDCA	Federal, Food, Drug, and Cosmetic Act
GAO	General Accounting Office
NCIMS	National Conference of Interstate Milk Shipments
USDA	U.S. Department of Agriculture

Introduction

In 1991 Americans, especially children, consumed billions of gallons of milk and milk products. Despite the assurances of federal, state, and industry officials that milk is one of the safest, most tested food products in the United States, concerns have been raised about the risks associated with milk contaminated with animal drug residues.

In December 1989 the Wall Street Journal reported the results of two surveys of animal drug residues in milk, one sponsored by the newspaper itself and the other sponsored by the Center for Science in the Public Interest, a consumer food safety and nutrition organization. The two surveys indicated that 20 and 38 percent, respectively, of retail milk samples tested may have contained animal drug residues, possibly including sulfamethazine—a suspected carcinogen—and other drugs that were not approved by the Food and Drug Administration (FDA). Both surveys used an analytical method called "Charm II." This method, which reportedly can detect the presence of seven classes of animal drug residues, generally cannot identify individual drugs within these classes and is therefore considered a multiresidue screening test. However, the method used may be overly sensitive to some drugs, and neither survey conducted further testing using more sophisticated methods to confirm the presence of any drug residues.

Concerned about such media reports of animal drugs (primarily antibiotics) contaminating the milk supply, FDA conducted a survey in 1990 to determine whether selected animal drug residues were present in milk. FDA stated that the results of its survey confirmed its belief that the nation's milk supply was safe and was not contaminated with unsafe animal drug residues.

However, we reported in November 1990 that FDA could not demonstrate that the nation's milk supply was free from unsafe animal drug residues because limitations in the survey methodology precluded any overall conclusions.[1] Even if the survey had been statistically valid, the results would still have been of limited use because FDA did not have test methods to detect and confirm many drugs believed to be used in milk-producing dairy cows (dairy cows). Except for penicillins, no routine testing was required to screen milk for such drugs, many of which are not approved for use in dairy cows. In addition, although the survey was not statistically valid, it showed instances of drug residues in milk, which suggested a need for more thorough examination by FDA to identify the types and amounts

[1]Food Safety and Quality: FDA Surveys Not Adequate to Demonstrate Safety of Milk Supply (GAO/RCED-91-26, Nov. 1, 1990).

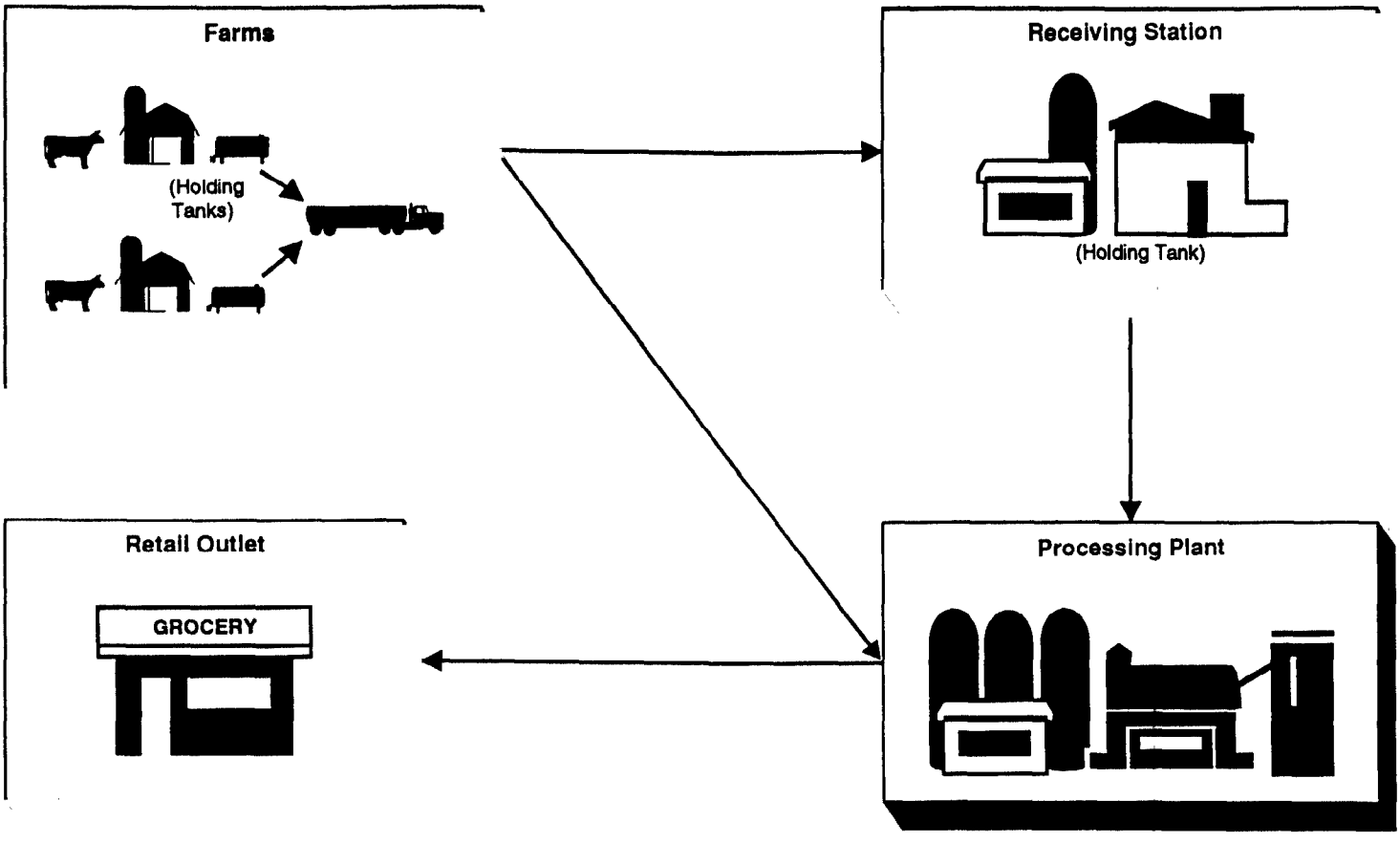
of animal drug residues that may be contaminating milk. Our report also raised questions about (1) the adequacy of routine monitoring of the milk supply by FDA and cooperating state agencies and (2) FDA's "extra-label use" policy, under which FDA will generally not take enforcement action against veterinarians for using drugs under certain conditions in a manner not specifically approved by FDA.

Milk Production and Distribution

Milk is about an $18.3 billion industry in the United States. In 1991 about 182,000 dairy farms in the United States, with about 10 million dairy cows, produced about 17 billion gallons of milk, and over 700 dairy plants produced fluid milk and milk products. According to dairy industry officials, better dairy management practices, including the use of animal drugs, have significantly increased milk production per cow over the last 40 years. Veterinarians and dairy farmers use animal drugs to treat disease or to control parasites in/on dairy cows. For example, penicillin, an antibiotic, is approved by FDA for treating dairy cows with mastitis, a common bacterial infection that leads to inflammation of cow udders. Animal drugs are also used to enhance reproduction of dairy cows.

Because milk is a highly perishable commodity, susceptible to bacterial contamination, it must be moved quickly from the dairy farm to the consumer. Figure 1.1 shows the route milk follows from the dairy farm to the retailer. Generally, dairy cows are milked by machine in the milking barn and the milk is pumped into the dairy farm's holding tank. A truck driver, certified by a state regulator but normally employed by a dairy processor, picks up the milk from dairy farm holding tanks, combining it with the milk from several other farms in a milk tanker truck. The milk is taken either directly to a processing plant or to a receiving station, where it is transferred to a large holding tank, combined with several other truckloads of milk, and delivered to a processing plant. The processing plant pasteurizes, packages, and ships the milk to retail outlets. While pasteurization provides a safeguard against disease transmission, it does not remove animal drug residues from milk. Because milk from several farms is commingled, unsafe and/or illegal animal drug residues from one dairy cow can contaminate a significant amount of milk. For example, in 1989 FDA estimated that treatment of just a single cow with sulfamethazine can contaminate the milk, when pooled, of 70,000 cows.

Figure 1.1: Route Milk Follows From Farm to Retailer



Animal Drug Regulation

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), FDA, part of the Department of Health and Human Services (HHS), is responsible for ensuring the safety of the milk produced in the United States each year, as well as numerous other food products. In addition, FDA is responsible for determining whether new animal drugs, such as antibiotics for use in dairy cows, are safe and effective for those animals and whether the food products, such as milk, derived from treated animals will be safe for human consumption. Under FFDCA and FDA policy, food items containing unapproved and/or harmful animal drug residues are considered to be adulterated and subject to enforcement action. FDA's Center for Veterinary

Medicine (CVM) is responsible for approving new animal drug applications, monitoring the distribution of animal drugs, and determining the safety of food products derived from animals treated with drugs.

Generally, FDA must approve new animal drugs before they may be legally marketed in the United States. Under FFDCA, animal drug sponsors must submit data to CVM to demonstrate that their products are safe and effective for their intended use(s). According to a CVM official, a typical new drug for food animals usually requires about 20 volumes of toxicology, pharmacology, residue chemistry, clinical trial, environmental assessment, manufacturing production, and other data. Generally, the data must be specific for each use and species of animal for which the drug is intended. On the basis of these data, FDA may approve an animal drug product labeled for a particular species, for a specific indication (use), at a stated dosage, by a certain method of administration (e.g., oral, topical, or injection) and, where appropriate, with applicable precautionary statements, warnings, and use restrictions. As of May 1992 FDA had approved 60 animal drugs for use on dairy cows.

For an animal drug product intended for use in a food-producing animal, sponsors must also demonstrate that the food products derived from treated animals are free of unsafe drug residues (including metabolites).[2] FDA establishes a tolerance—a legally binding limit—to define the amount of residues of a new animal drug in food products that is demonstrated to be safe in the human diet. FDA has established tolerances in milk for 16 of the 60 drugs approved for use in dairy cows.[3] FDA also sets withdrawal periods and milk discard times for approved drugs, during which time meat or milk, respectively, from treated dairy cows cannot be marketed. These withdrawal periods are necessary to allow the drugs to deplete from the animals' systems so that any residues are below the tolerance level. According to FDA, the withdrawal period or the milk discard time is the interval between the time of the last administration of a drug and the time the dairy cow can be safely slaughtered for food or the milk can be safely consumed. Generally, withdrawal times range from several hours to several weeks, and milk discard times range from zero to 96 hours. If the

[2]Drug compounds administered to food-producing animals can be formed or broken down into substances (metabolites and degradation products of the compound) by the animal's biological systems. These products can pose toxicological concerns of their own. Therefore, the total residue of a drug proposed for use in food-producing animals consists of the parent drug and its metabolites and any other substance formed in or on food as a result of the use of the parent compound.

[3]FDA has not established tolerances for many drugs approved for use in dairy cows because some drugs were approved years ago on the basis of data that indicated that no safety problem would result from use of the drug, or because FDA determined that no residues of concern would result even if there was no milk discard time (e.g., the drug was approved for topical use only).

withdrawal and milk discard times are not adequate, not specified on the label, or not followed, illegal and/or potentially unsafe residues may result in tissue and milk. Illegal animal drug residues are those that either are not allowed to be present in tissue or milk or are present in an amount greater than the amount allowed by an FDA-established tolerance.

When tolerances do not exist or cannot be calculated because the necessary data are not available, FDA may set "safe levels" for drug residues. Safe levels are not official tolerances and do not represent FDA approval of the drug use or resulting residues. Rather, these values represent an informal level of safety that FDA uses to determine when residues may pose a health risk. FDA also uses safe levels as a target for developing analytical methods to monitor unapproved uses and to help set priorities for possible regulatory action against those who illegally use a drug. Generally, FDA estimates safe levels on the basis of tolerance levels established for a drug in other animal species and tissues. For milk, FDA estimates the safe level that corresponds to one-third or one-tenth of the lowest published tolerance for the drug residue in other animal species and tissues, depending on the acceptability of available toxicology data, or the lowest level of the drug residue that can be quantified by an analytical method. As of May 1992 FDA had estimated safe levels in milk for residues of 12 drugs either not approved for use in dairy cows or used in an unapproved manner. For one drug, chloramphenicol, FDA has determined that no safe level can be established because of concerns about its safety in human food.

For drugs approved for use in food-producing animals, the sponsor must develop an analytical method, called a "regulatory method," to detect and measure residues that might be present in food products derived from treated animals. Sponsor-proposed regulatory methods must be validated under formal FDA laboratory procedures before FDA approves the drug. In contrast to multiresidue screening test methods, sponsor-submitted regulatory methods typically can detect and quantify the presence of individual drugs but usually only for a single, specific drug; the tests are therefore considered single-residue methods.

Under FFDCA the actual or intended use of an animal drug in a manner inconsistent with its approved labeling is illegal and can result in FDA's taking regulatory action against the veterinarian, dairy farmer, or other persons involved. However, exercising its discretionary enforcement authority, CVM has established guidelines for veterinarians to treat food-producing animals not in accordance with approved labels (i.e.,

extra-label use), if suffering and/or death would result from not treating the affected animal. In establishing what is known as the extra-label use policy, CVM stated that it would ordinarily refrain from taking regulatory action against licensed veterinarians for using or prescribing drugs in violation of FFDCA provided certain conditions are met. CVM's policy does not permit nonveterinarians (e.g., dairy farmers) to treat food-producing animals with drugs in an unapproved manner. In addition, CVM has declared that certain drugs, such as chloramphenicol, cannot be used under the extra-label use policy. (See ch. 4.)

FFDCA also requires that the labels on animal drug products contain adequate directions for use. Products for which adequate directions for use can be written for the lay person are labeled for over-the-counter use. By regulation, FDA has established that if adequate directions for use cannot be written for the lay person, then use of the product may be restricted to state-licensed veterinarians and labeled for prescription use only. In addition, although veterinarians may determine animal drug treatments, dairy farmers—or their employees—typically administer animal drugs.

While FDA is responsible for monitoring animal drug residues in milk, the U.S. Department of Agriculture (USDA) is responsible for monitoring drug residues in meat and poultry products. USDA's Food Safety and Inspection Service collects information on animal drug residues in meat tissues on all classes of animals that are slaughtered in federally inspected plants, including dairy cows that are removed from milking (culled) and sent to slaughter.

Milk Safety Regulation

Under the Public Health Service Act, FDA administers the Interstate Milk Shippers Program—a voluntary federal/state program established to ensure the safety and wholesomeness of fresh milk and cream in the United States. FDA's milk safety program is a collaborative federal/state effort that dates back to the mid-1920s. The program was established after the Public Health Service, FDA's parent organization within HHS, developed the 1924 Standard Milk Ordinance to assist states and municipalities in developing effective sanitation programs to prevent the transmission of milk-borne diseases. The Public Health Service called for state and local milk control agencies to voluntarily adopt the ordinance.

To provide for uniform interpretation of this ordinance, an accompanying code was published in 1927. This milk regulation, now entitled the Grade A

Pasteurized Milk Ordinance (Milk Ordinance), has undergone numerous revisions since that time and is the basic milk sanitation standard used today in the voluntary, cooperative interstate milk safety program in which all 50 states, the District of Columbia, and Puerto Rico participate. Under the Milk Ordinance, only Grade A milk can be used for fluid consumption and marketed in interstate commerce.

Under the Interstate Milk Shippers Program, the states have reciprocal agreements whereby shipments of Grade A milk are accepted regardless of their origin. In order for a dairy farmer to qualify as a Grade A producer, cooperating state agencies inspect and rate the producer's facilities and milk according to the provisions of the Milk Ordinance. FDA publishes a quarterly list of milk shippers approved for interstate commerce. Most milk (over 90 percent) produced and marketed in the United States is Grade A.

The National Conference on Interstate Milk Shipments (NCIMS), established in 1950, is a voluntary organization of state officials that, along with FDA and the dairy industry, oversees the cooperative program. NCIMS, which meets every 2 years, deliberates on changes to the cooperative program and the Milk Ordinance. NCIMS most recently met in April 1991. NCIMS' only voting delegates are representatives of state regulatory agencies. Although industry and FDA representatives do not vote on changes to the ordinance, industry participates and FDA retains final veto authority on any proposed changes.

Under a memorandum of understanding between FDA and NCIMS, the states generally carry out most monitoring, enforcement, and other regulatory functions required by the Milk Ordinance, and FDA ensures that all states are complying with the rules and regulations of the cooperative program. The Milk Safety Branch in FDA's Center for Food Safety and Applied Nutrition (CFSAN) is primarily responsible for directing FDA's activities under the program. Milk specialists in FDA's six regional offices, which report to FDA's Office of Regulatory Affairs, handle the day-to-day interaction with state milk control officials. FDA's responsibilities under the Interstate Milk Shippers Program include, among other things, selectively inspecting dairy farms and plants,[4] evaluating the adequacy of state milk programs, and certifying state regulators to conduct dairy farm and plant inspections. In addition, CFSAN's Laboratory Quality Assurance Branch

[4]These inspections, called "check ratings," are limited inspections of dairy farms and processing plants intended to ensure the integrity of state programs.

evaluates and certifies state laboratory facilities and procedures for testing drug residues in milk.

State milk control officials or their representatives inspect all Grade A dairy farms every 6 months and dairy plants every 3 months to ensure that the requirements of the Milk Ordinance—primarily sanitation requirements—are being met. As part of the farm inspection, state officials examine the dairy farm milk house, milking barn, or stable to ensure, among other things, that unapproved and/or improperly labeled animal drugs are not used or stored in those areas. When inspecting dairy plants, state officials review records of the plants to ensure that required testing is carried out. The state can take regulatory action if a dairy farm or dairy plant fails an inspection. For example, dairy plants that fail an inspection can no longer ship Grade A pasteurized milk in interstate commerce until they pass a subsequent inspection.

The Milk Ordinance provides minimum standards that milk producers must maintain for Grade A certification. States are required to ensure that raw milk samples collected from the holding tanks of all individual Grade A farms four times every 6 months are tested to check for compliance with Milk Ordinance standards on bacterial counts, somatic cell counts (increased cell counts indicative of infection), and animal drugs. Some states, such as Wisconsin, have delegated residue testing required under the Milk Ordinance to the dairy industry. When testing reveals that a milk sample contains drug residues above legal limits, the milk contaminated with drug residues must be disposed of in a manner that removes it from the human or animal food chain.

Before NCIMS revised the Milk Ordinance in April 1991, the only official test for detecting animal drugs in milk was the Bacillus Stearothermophilus Disk Assay test (disk assay). While the disk assay effectively detects residues of four drugs in the beta lactam family (including penicillin), it is much less effective in detecting many of the other drugs now being used by the dairy industry. The 1991 revisions to the Milk Ordinance included provisions to expand both the number of official test methods used and the number of animal drugs tested for. These revisions and other recent federal, state, and industry initiatives to improve milk safety are discussed in chapter 2.

Risks of Drug Residues in Milk

Scientists disagree over the threat to human health presented by animal drug residues in milk, especially at barely detectable levels. The Center for

Science in the Public Interest believes that some animal drug residues may present an unnecessary health risk. According to some scientists, low levels of some animal drugs in food may produce (1) allergic reactions in persons sensitive to antibiotics; (2) the development of bacteria resistant to antibiotics; (3) the suppression of the human immune system through constant exposure to low levels of antibiotics; and (4) a slight increased risk of adverse chronic effects, such as cancer. In particular, there are reports in the medical literature of the emergence of antimicrobial-resistant bacteria linked to the use of antibiotics on dairy cows, which could increase the risk of human infection.[5] In addition, FDA policy guidelines state that illegal drug residues in the food products of treated animals can constitute a health hazard to people who consume the food.

Nevertheless, some international studies have concluded that the small amounts of animal drug residues that may be found in food are not likely to cause a serious health hazard to humans. Furthermore, FDA officials believe that microbial pathogens, such as bacteria, are a more serious food safety problem than animal drug residues. However, some scientists believe that the potential health risks of even minute exposures to low levels of some animal drug residues over several years are unknown.

Objectives, Scope, and Methodology

The Chairman of the Human Resources and Intergovernmental Relations Subcommittee, House Committee on Government Operations, asked us to review federal and state efforts to test and control animal drug residues in milk and to examine FDA's extra-label use policy. To accomplish these objectives, we gathered information from FDA headquarters, FDA regional milk specialists, selected state regulatory agencies, USDA headquarters, animal drug and milk industry officials, and veterinarians.

At FDA headquarters we interviewed and obtained data from officials from CFSAN's Milk Safety Branch and Laboratory Quality Assurance Branch; the Office of Regulatory Affairs; and CVM's Office of Surveillance and Compliance, Office of Science, and Office of New Animal Drug Evaluation. We also discussed with CVM officials the extra-label use policy, the available information on the animal drugs actually used by dairy farmers, the status of methods to detect animal drug residues, and the measures FDA uses to ensure that the milk supply is free of illegal and/or unsafe animal drug residues. We also surveyed regional milk specialists in each of

[5]Caroline A. Ryan, et al., "Massive Outbreak of Antimicrobial-Resistant Salmonellosis Traced to Pasteurized Milk," Journal of the American Medical Association, vol. 258, Dec. 11, 1987, pp. 3269-74.

the six FDA regions for overall information on state testing and sampling programs.

We attended the April 1991 session of NCIMS and the July 1991 and February 1992 NCIMS Executive Board meetings for information on the changes to the Milk Ordinance and joint FDA and state programs.

We gathered information on state milk regulatory programs and visited selected dairy farms, animal feed stores, cooperatives, and milk-processing plants in California, Wisconsin, New York, and Florida. We also conducted phone interviews with state milk regulatory officials from Minnesota, Texas, and Pennsylvania. We chose these seven states on the basis of geographic location and because they produced almost 60 percent of the nation's milk in 1991. However, we did not examine state controls over rejected milk to see if it was disposed of in accordance with the Milk Ordinance.

At USDA headquarters we interviewed officials from USDA's Food Safety and Inspection Service, Animal and Plant Health Inspection Service, Agricultural Research Service, and Economic Research Service. We obtained information on USDA's method of compiling data on drug residues found in tissues of food-producing animals and on various USDA-sponsored programs to reduce and detect drug residues in animal tissues. We also gathered statistics on the amount and value of milk produced and consumed in the United States.

We compiled a list of animal drugs believed to be used on dairy cows from multiple sources, including a list of drugs approved for use on dairy cows from CVM officials. We also compiled a list of unapproved drugs believed to be used on dairy cows from multiple sources, including FDA check-rating data, FDA National Drug Residue Milk Monitoring Program information, and a list of drugs CVM compiled to set priorities for the development of methods to detect residues of these drugs in milk. In addition, we also used information from USDA on tissue residues in slaughtered dairy cows and USDA's Food Animal Residue Avoidance Databank, a data base that contains information on those animal drugs and chemicals with the potential to cause residues in food.

We analyzed information on test methods for detecting animal drug residues in milk on the basis of information from CVM, the AOAC International and its subsidiary the AOAC Research Institute, the Virginia Polytechnic Institute and State University, and manufacturers of the tests.

We then compared this information with the list of approved and unapproved animal drugs to determine how many animal drugs the test methods claimed to detect in milk.

We also interviewed officials from the Animal Health Institute, National Milk Producers Federation, Milk Industry Foundation, National Dairy Promotion and Research Board, and Center for Science in the Public Interest. We obtained information on the dairy industry's efforts to reduce and detect drug residues in milk. At the Center for Science in the Public Interest, we obtained information to characterize possible human health risks associated with animal drug residues.

Finally, we interviewed officials from the American Veterinary Medical Association and American Association of Bovine Practitioners, as well as several private veterinarians. Among other things, we obtained information on FDA's extra-label drug use policy, the extent to which the policy is being used, and the availability of animal drugs to dairy farmers.

We conducted our review from November 1990 through November 1991, with updates through July 1992, in accordance with generally accepted government auditing standards. As requested, we did not obtain written agency comments on a draft of this report. We did, however, discuss the factual content of the report with FDA officials, state and industry organizations, and the American Veterinary Medical Association. In general, these groups agreed with the factual information or provided additional technical or clarifying details that we added where appropriate. In addition, all groups generally stated that they believed that substantial progress had been made in the past few years to improve monitoring of the milk supply or to provide for more careful and knowledgeable use of animal drugs. Among the changes cited were more awareness of the problem and its potential consequences both in health and safety and economic terms. Furthermore, these groups cited as major improvements the 1991 revisions to the Milk Ordinance, additional voluntary testing by the industry, and the development of an industry quality assurance program aimed at more responsible drug use at the farm level.

On the other hand, almost all of the groups expressed varying degrees of frustration at the lack of leadership and progress in some areas. The areas cited differed depending on what part of the dairy or animal health industry the groups represented. For example, veterinarians are frustrated because of what they view as a lack of approved, effective animal drugs to treat dairy cows, while animal drug companies are concerned about the

lack of an expedited FDA process or initiative to either extend some uses or approve new uses. In addition, veterinarians believe that they have sufficient information to make extra-label use decisions. However, producers and processors are frustrated because they view the milk supply as safe and cannot demonstrate it and expressed concern that FDA's extra-label use policy allows the uncontrolled use of animal drugs that can give their products a bad reputation. Producers believe that any extra-label use should be done only within the context of a quality assurance program that emphasizes a strong veterinarian/client/patient relationship and includes appropriate record keeping. Both states and processors expressed frustration that FDA continues to develop laboratory-based test methods that do not respond to their needs for reliable, inexpensive screening tests that can be used in the field. Where appropriate we made changes on the basis of these discussions and believe that the report is a fair and accurate presentation of the issues.

Use of Approved and Unapproved Drugs on Dairy Cows Is Widespread

On the basis of state testing, FDA estimated that up to 1 percent of the nation's milk supply was contaminated with excess animal drugs in 1991 and was discarded. The actual extent of contamination may have been greater because, under the Milk Ordinance, the states are monitoring milk for only 4 of the 82 animal drugs known to be or suspected of being used on dairy cows that have the potential to leave residues in milk. Recognizing the long-standing gap between animal drug usage and testing—and in response to our 1990 report and other criticisms—FDA, the states, and the dairy industry have initiated several actions aimed at closing this gap.

Gap Between Animal Drug Usage and Testing Is Long-Standing

A long-standing gap has existed between the number of animal drugs believed to be used in/on dairy cows and the number of drugs FDA and the states have tested for in milk. Since July 1980 the only official test method for monitoring animal drug residues in milk and taking regulatory action, under the Milk Ordinance, has been the Bacillus Stearothermophilus Disk Assay test (disk assay) which can detect residues of only four animal drugs in milk at their tolerance or safe levels: ampicillin, cephaparin, hetacillin, and penicillin. However, the method is much less effective in detecting many other drugs at levels permitted by FDA—such as sulfas and tetracyclines—that are believed to be used on dairy cows. For instance, the disk assay detects sulfa drugs at levels of 15 parts per million or higher—1,500 times the 10 parts per billion safe level set by FDA for milk.

FDA is aware that veterinarians and dairy farmers may choose to use certain animal drugs specifically because they know that regulators cannot detect or are not checking for that drug. The unapproved use of drugs on dairy cows can result in residues in milk that pose a risk to consumers because the studies necessary to show the proper milk discard times to avoid residues or the safety of possible residues are generally not available.

FDA officials estimated that in 1991 the states annually tested at least 1.2 million samples of raw milk using the disk assay for antibiotics. On the basis of these tests, FDA estimated that up to 1 percent of the nation's milk supply was contaminated with antibiotic residues above FDA-permitted levels and had been discarded. However, the true extent of contamination is not known because under the Milk Ordinance the states test for only 4 of the 82 animal drugs known to be or suspected of being used on dairy cows. Some states and parts of the milk industry have supplemented the testing required under the Milk Ordinance with screening and other test

methods. For example, according to a 1990 survey by the Milk Industry Foundation, its members, who represent most of the fluid milk processors, conducted over 2 million tests of raw milk with several multiresidue screening tests for a variety of drug residues. While the industry found a very low level of drug residues, there are problems in determining the precise level because of computational and other difficulties, such as double counting of test samples. Neither FDA nor the states have collected data from the results of supplemental tests in a uniform manner that would allow analysis. In addition, scientists disagree on the use and reliability of some of these methods (see ch. 3).

Reliable information on the extent to which veterinarians and others use unapproved drugs to treat dairy cows is unavailable. Consequently, the exact number of animal drugs used on dairy cows that might show up as residues in milk is not known. However, in an attempt to find out what drugs may be used on dairy cows with the potential to leave residues in milk, we compiled a list of drugs from multiple sources, including data from FDA's check ratings; state surveys of dairy farm practices; observational data from dairy farms we visited; interviews with dairy farmers, veterinarians, and dairy industry officials; and private market sales research data. In addition, we also used information from USDA on tissue residues in slaughtered dairy cows and USDA's Food Animal Residue Avoidance Databank, a data base that contains information on animal drugs and chemicals with the potential to cause residues in food. We compared this list with available FDA compliance and surveillance data, including data gathered from FDA officials' informal networking in the veterinarian community, adverse drug reaction reports, and complaints from farmers and veterinarians. We also compared our list against the drugs that FDA is testing for on a limited basis and has developed or plans to develop methods to test for residues in milk.

We identified 82 animal drugs known to be or suspected of being used on dairy cows (30 approved and 52 unapproved for use on dairy cows) that may leave residues in milk (see app. I). CVM officials reviewed our list of drugs and generally agreed that the drugs listed are used to treat dairy cows, but the frequency of use and potential health risks of potential residues in milk vary among the drugs listed. Available CVM compliance and surveillance data, as well as information from CVM's test method development activities, indicate that 64 (29 approved and 35 unapproved for use on dairy cows) of the 82 drugs on our list are commonly used on dairy cows or these drugs may leave residues in milk that could pose a potential health concern to consumers. Specifically, FDA's data indicates

that 57 of these 82 drugs are commonly used, and 7 others may leave residues that raise health concerns. These same data indicate that the remaining 18 drugs are used infrequently on dairy cows.

Our list of 82 drugs is not a definitive list; the actual number or combination of drugs used in an approved or unapproved manner on dairy cows could be larger or smaller. Regardless of the actual number, however, CVM officials agree with us that all available evidence continues to indicate a significant gap between the number of animal drugs used on dairy cows, especially those not approved for such use but commonly used, and the number of drug residues that the states are testing milk for under the Milk Ordinance. Furthermore, according to the director of USDA's residue testing program, USDA continues to be concerned about the use of drugs not approved for treating dairy cows sent to slaughter.

Although FDA approves animal drugs for specific species and uses, dairy farmers and veterinarians have access to a wide range of over-the-counter and prescription animal drugs that they could use both legally and illegally on dairy cows. According to officials from FDA and the American Veterinary Medical Association (AVMA), dairy farmers and veterinarians use unapproved drugs to treat dairy cows because the range of approved drugs is not adequate to treat the many diseases that afflict dairy cows. According to a CVM official, about 80 percent of animal drugs intended for use in food-producing animals are approved for over-the-counter sale. CVM and AVMA officials believe that most misuse of animal drugs in food-producing animals, including dairy cows, results from the unapproved use of over-the-counter drugs by farmers.

Over-the-counter drugs provide dairy farmers and others access to a wide range of drugs. For example, in June 1991 we purchased several over-the-counter animal drugs from a store run by a large dairy processing plant that sells products primarily to dairy farmers. Among our purchases was a gallon of nitrofurazone solution labeled for use on dogs, cats, and horses as a topical treatment for sores. The label warned against using the drug on horses intended for food; however, FDA and state officials suspected that dairy farmers and veterinarians were injecting nitrofurazone into dairy cows to carry many other drugs into the cows' systems to treat mastitis. In August 1991 FDA specifically banned any unapproved or extra-label use of nitrofurazone on food-producing animals because, among other things, it is a suspected carcinogen. However, the product we purchased is still available over the counter for its labeled uses.

Dairy farmers can also obtain animal drugs for use on dairy cows from veterinarians. However, according to FDA officials, FDA continues to receive reports from consumers, industry officials, and some veterinarians of illegal prescription sales. In addition, under CVM's extra-label use policy, FDA will ordinarily not pursue enforcement action when a veterinarian violates the law by treating a food-producing animal with a drug not approved for the animal, and/or not approved for the particular manner in which used, if the animal's life is in danger and certain conditions are followed. For example, a veterinarian could use or prescribe a drug approved for use only on nonfood-producing animals to treat dairy cows under certain conditions (see ch. 4). However, sometimes not all the conditions of the policy are followed. For example, at a large dairy farm we visited, a veterinarian, employed by a drug distributor, who seldom visited the dairy farm, left the farmer with a list of animal drugs that could be ordered in unlimited quantities over the phone for months at a time. The list included instructions for using some of these drugs in an extra-label manner on dairy cows. CVM and AVMA officials said that this was a "blanket" drug prescription that does not meet the criteria for a valid veterinarian/client/patient relationship—a key condition of CVM's extra-label use policy. (The criteria for a valid veterinarian/client/patient relationship are described in app. II.)

FDA and Others Have Taken Actions to Close the Gap

In recognition of the long-standing gap between drug usage and testing, FDA, the states, and industry have taken actions to close the gap as a result of recommendations we and others have made. This section provides a brief overview of these recent actions, including the revisions to the Milk Ordinance as well as FDA efforts to conduct its own monitoring program. However, as discussed in chapter 3, limited progress has been made in implementing these actions.

Revisions to the Milk Ordinance

In April 1991 FDA, the states, and industry revised the Milk Ordinance to increase state and industry monitoring and surveillance of animal drug residues in milk. Specifically, the revisions were intended to increase the number of milk samples analyzed, drug residues tested for, and test methods the states and industry could use for milk monitoring and regulatory purposes. Implementation of the revisions involves multiple parties and responsibilities and a two-phase schedule.

In the first phase, which began in January 1992, the dairy industry, for the first time, was required to sample and test raw milk from all milk tankers

as they enter dairy plants for beta lactam drugs, a class of antibiotics that includes penicillin. Industry is also required to begin testing, on a selective basis, for additional drug residues, when FDA determines that such residues are a concern. In addition, industry is required to keep records on all tests conducted in a 6-month period and report all residues detected to state regulators, even for tests conducted for its own purposes.

In the second phase, which began in July 1992, state regulators are responsible for monitoring industry's compliance with the new testing requirements by making unannounced, quarterly on-site inspections of processing plants to collect samples from milk tankers and to review industry records of the testing conducted. Also, as of July 1992 the states are to take regulatory action on all positive screening test results. According to the revised Milk Ordinance, a result is considered positive when residues exceeding the tolerance and/or safe levels established by FDA are detected using a method that has been evaluated and deemed acceptable by FDA to detect drugs at those levels. In addition, the revisions provide for more specific state-enforced penalties when illegal animal drug residues are found in milk. The Milk Ordinance revisions changed the basic minimum testing requirements for the states only in that state testing is now intended to serve as an audit of industry screening tests rather than the principal monitoring mechanism. States are still required to ensure that raw milk samples from all individual Grade A farms are sampled and tested four times every 6 months, in at least 4 separate months, for beta lactam residues and other animal drug residues to be specified by FDA.

Under the revisions FDA is responsible for identifying additional drugs to be tested for, notifying state regulators of animal drug tolerances and/or safe levels, recommending additional screening test methods for the states and industry to use, and certifying state laboratories. The Milk Safety Branch within FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for coordinating FDA's activities with the National Conference on Interstate Milk Shipments (NCIMS) to implement the revisions to the Milk Ordinance. CVM is the lead unit responsible for identifying additional drugs to test for, establishing tolerance and/or safe levels, evaluating and recommending additional test methods, and working with the AOAC Research Institute to evaluate new screening test methods. In addition, CFSAN's Laboratory Quality Assurance Branch is responsible for training and certifying state officials on the provisions of the program. In turn, certified state officials are responsible for training and certifying over 1,000 dairy plant supervisors and employees.

To meet the revised Milk Ordinance testing requirements, states and industry are required to use screening methods to test for beta lactam drug residues that (1) were officially sanctioned by AOAC International at the time the ordinance was revised; (2) are evaluated by the AOAC Research Institute (a nonprofit subsidiary of AOAC International) and accepted by FDA; or (3) are accepted by FDA to be equally accurate, precise, and practical.[1] Four multiresidue screening tests met these requirements at the time the ordinance was revised and have thus been incorporated into the ordinance: the disk assay, Charm I, Charm II (liquid), and Delvo P. According to FDA officials, these test methods may undergo further evaluation, depending on the outcome of the new AOAC Research Institute/FDA program to evaluate screening test kits.

Rather than specify methods in addition to the disk assay for the states and industry to use, the revisions to the Milk Ordinance provided a procedure for adding new or revised screening methods that are evaluated by the AOAC Research Institute and accepted by FDA. Screening methods may be submitted to a new, special program for expedited evaluation and annual recertification. The AOAC Research Institute is to evaluate screening test methods, called test kits, to provide an independent third-party review of manufacturers' performance claims for test kits intended to detect or measure animal drug residues in milk. FDA is to review the Institute's evaluation of each method and determine whether the method is acceptable for regulatory purposes under the Milk Ordinance. The methods submitted to the AOAC Research Institute must be capable of detecting drug residues at the tolerance and/or safe levels established by FDA to be recommended for use under the Milk Ordinance. The program was intended to be a "fast-track" approach (90 days) for evaluating the performance of screening methods.

Also, as of July 1992 dairy farmers are required to participate in the Milk and Dairy Beef Residue Prevention Protocol when drug residues found in their milk products exceed permitted levels. This education program for dairy farmers and veterinarians, developed by the National Milk Producers Federation and AVMA, is aimed at improving animal husbandry practices and ensuring proper animal drug use.

Other Actions

In 1990 we recommended that FDA develop more complete information on the incidence of animal drug residues in milk. We suggested that FDA ask

[1]In addition, until FDA recommends additional screening test methods, industry may use any of 14 multiresidue screening tests that are capable of detecting beta lactam drugs as demonstrated in a 1991 study conducted by the Virginia Polytechnic Institute and State University.

the states and the dairy industry to routinely provide the results of their screening tests for drug residues in milk, as well as information on sampling plans and the types and sensitivities of the test methods they employed. FDA concurred with our recommendation and plans to develop a national data base to collect results of state and industry milk sample tests. In addition, in February 1991 FDA established the National Drug Residue Milk Monitoring Program to provide information on the nature and extent to which animal drugs may be contaminating the nation's milk supply. For the first time, FDA began to routinely test samples of raw milk for selected animal drug residues.

Because many of the drugs suspected of being used on dairy cows are not approved for such use, manufacturers of those drugs are not required as part of FDA's approval process to develop tests to detect the residues of their drugs in milk. However, other companies have developed and sell screening tests that claim to detect some of these drugs. Our 1990 report recommended that FDA work with the states to evaluate these commercially available screening tests and encourage NCIMS to supplement the disk assay in the Milk Ordinance with those tests found to be effective for sulfa and other animal drugs. We also recommended that FDA set priorities for and expedite its efforts to develop and evaluate new test methods for animal drug residues in milk, possibly according to the health risks associated with the individual drugs involved. FDA concurred with our recommendations. In December 1990 FDA announced a program to evaluate commercially available screening methods for chloramphenicol, sulfonamides, gentamicin, and tetracyclines. Furthermore, FDA increased its efforts to develop methods to detect animal drugs in milk for regulatory enforcement purposes.

The recent FDA, state and dairy industry actions to close the gap between drug usage and testing appear promising. However, effectively implementing these actions involves the close coordination and actions of several organizations. Also, this implementation involves complex and sometimes contentious issues, including the reliability of new test methods for animal drugs. Success will therefore depend heavily on effective FDA leadership in planning, coordinating, and implementing these efforts. As discussed in the following chapter, this leadership has not yet materialized, and progress in improving monitoring efforts has been limited.

Poor Planning and Testing Limitations Inhibit Progress in Improving Milk Monitoring

The National Conference on Interstate Milk Shipments (NCIMS) revised the Milk Ordinance in April 1991 to improve drug residue monitoring. However, the states are generally testing milk for only the same 4 animal drugs as they were in 1980, while up to 82 drugs that may leave residues in milk are known to be or are suspected of being used on dairy cows. While the dairy industry is testing for a larger, but undefined number of drug residues than the states, delays in implementing the revisions to the Milk Ordinance are impairing federal and state oversight of industry safety assurance efforts. Implementing the revisions is proving difficult to achieve because of their complex and time-consuming nature and the extensive coordination and cooperation needed among the multiple players. The revisions are behind schedule and the outcome of a new screening method evaluation program—a critical element—is uncertain. This lack of progress has occurred primarily because of (1) ineffective FDA leadership in planning and coordinating implementation efforts and (2) unresolved differences in the types and extent of testing needed for detecting drug residues in milk. Progress could be enhanced by developing a comprehensive strategy for monitoring animal drugs in milk that integrates the multiple players involved; defines roles and responsibilities; outlines the optimum sampling and testing scheme to deter drug misuse while considering limited federal and state resources; and provides for resolution of issues surrounding testing methods that the states and industry may use under the Milk Ordinance. Until these issues are resolved, FDA and the states cannot provide the necessary oversight of industry efforts to ensure consumers that the nation's milk supply is free of excess animal drug residues that may pose potential health concerns.

Finally, FDA's National Drug Residue Milk Monitoring Program (monitoring program) has statistical limitations that preclude drawing any conclusions about the incidence of drugs in milk and raise questions about the utility of the program, especially considering anticipated expanded state and industry testing under the revised Milk Ordinance.

Implementation of Milk Ordinance Revisions Behind Schedule and Uncertain

Implementing the revisions to the Milk Ordinance has proven to be more difficult than participants at the April 1991 NCIMS conference had anticipated. In particular, developing the new joint AOAC Research Institute/FDA program to evaluate screening methods for use under the Milk Ordinance has been more complex, time consuming, and costly than initially envisioned. NCIMS officials initially estimated that the first round of screening methods evaluated and accepted under the new program would be complete by July 1, 1992, in time to coincide with the effective date of

new state monitoring responsibilities. However, the AOAC Research Institute and FDA are still developing program procedures and evaluation criteria. In addition, the program has encountered unanticipated obstacles. Until the program is in place, the gap between drug usage and testing will continue to exist and government oversight of industry testing efforts will be limited.

Early lack of agreement between officials from FDA and the AOAC Research Institute delayed the start-up of the program. Initially, the program was to involve a sequential process: the Institute was to evaluate screening methods and then FDA was to review the Institute's results and recommend methods for use under the Milk Ordinance. Following the NCIMS conference, the AOAC Research Institute established a task force to develop the expedited program to review screening methods. However, just before the Institute was to announce the program in February 1992, an official in FDA's Center for Veterinary Medicine (CVM) informed the Institute that CVM disagreed with the proposed program procedures, effectively putting the program on hold. According to this official, concurrent Institute and FDA evaluation of screening methods would be more efficient and would minimize the chance that FDA would reject methods that the Institute had favorably evaluated because of differences in scientific judgment or because a method was not suitable for regulatory use under the Milk Ordinance. As a result, in March 1992 CVM and the Institute agreed to negotiate a joint effort to establish procedures and criteria for evaluating and recommending screening methods to satisfy the requirements under the revised Milk Ordinance.

However, the implementation date of this program is still uncertain. As of July 1992, over a year after the Milk Ordinance was revised, FDA and the AOAC Research Institute had not yet formally signed a memorandum of understanding for the program. In addition, FDA and Institute officials were still developing the procedures for the program to accommodate the concerns and needs of FDA, the states, the milk industry, test kit manufacturers, and the Institute. In particular, test kit manufacturers were concerned about the costs involved and the preliminary procedures, which they thought were more burdensome and time consuming than what had been envisioned when the program was first proposed. As of July 1992, the Institute estimated that it would be fall 1992 before it can begin evaluating the first round of screening test methods. As a result, additional methods will not be available until sometime in 1993 at the earliest. Even then, the laboratory branch in FDA's Center for Food Safety and Applied Nutrition (CFSAN) will have to train and certify state officials, who in turn must train

and certify industry supervisors before the newly accepted screening methods may be used for regulatory purposes. This process will take several more months.

Moreover, the outcome of the program is also uncertain because it is an unprecedented venture. The AOAC Research Institute has been trying to develop a completely new program to sanction screening methods that differ from the analytical methods santioned by its parent organization, AOAC International. The new program will not qualify screening methods as AOAC official methods, a qualification which typically takes several years to achieve through AOAC International's interlaboratory collaborative process. Furthermore, FDA does not have the legislative authority to approve or sanction screening methods that are not submitted as part of a sponsor's application for a new animal drug approval, according to the Deputy Director of CVM. Because of their distinct, independent missions—AOAC Research Institute established for standard-setting purposes and FDA established for regulatory purposes—neither organization is bound to accept the decisions and positions of the other. Consequently, successful implementation of the Milk Ordinance revisions, aimed at increasing the number of screening methods for milk monitoring, depends on the successful development of this novel program between FDA and the AOAC Research Institute and the participation of test kit manufacturers.

Other obstacles have arisen. For example, certification of state laboratories to run the three new screening methods for selected beta lactam drugs that were added to the Milk Ordinance has been delayed. According to the Chief of CFSAN's Laboratory Quality Assurance Branch, the states are postponing decisions on what screening methods to buy pending the outcome of the AOAC Research Institute/FDA program for evaluating screening methods and, in part, because of the financial burden in purchasing these methods. In addition, the laboratory branch has postponed training state laboratory officers to certify industry plant supervisors until the screening method program is in place and the first methods are accepted. As a result, the states generally continue to test for the same four drugs using the disk assay that they have been testing for over the past 12 years.

FDA Has Not Effectively Managed Implementation of the Revisions

Although the revisions to the Milk Ordinance are proving difficult to implement, FDA has not effectively planned and managed their implementation. Initial efforts to implement the revisions were impeded by a lack of internal FDA communication, coordination, and agreement. Furthermore, lack of a clear FDA action plan has created unnecessary frustration and confusion for industry and the states and delayed progress.

State and AOAC Research Institute officials have voiced concerns about the lack of coordination and communication within FDA between CVM and CFSAN's Milk Safety Branch on interpreting and implementing the Milk Ordinance revisions. For example, AOAC Research Institute officials were confused and temporarily halted their efforts to develop the new screening method evaluation program when they received conflicting information from the Milk Safety Branch and CVM on whether FDA would accept the Institute's proposed procedures to evaluate test methods. The Milk Safety Branch and CVM learned about their differences with each other not from internal coordination but from AOAC Research Institute officials. In addition, some state officials have been unable to obtain authoritative answers from various FDA offices on questions about FDA's interpretations of the revisions because of the lack of internal agreement among FDA offices. The Chief of the Milk Safety Branch acknowledged that there is a communication problem between his branch and CVM. According to the Chief, CFSAN proposed creating a task force to facilitate communications between the offices in February 1992. In May 1992 FDA created the Milk Working Group to establish formal links between CFSAN and CVM on a management level and to formulate agency consensus on policy issues related to animal drug residues in milk and dairy foods. The group held its first meeting in June 1992 and plans to meet monthly.

In some cases FDA has not yet developed plans and procedures for enacting the revisions. For example, industry was required to begin retaining and reporting residue data to the states in January 1992, and the states were required to begin auditing these data in July 1992. However, the start-up of a national data base has been delayed, in part, because of FDA resource constraints. FDA's Office of Federal/State Relations within the Office of Regulatory Affairs, in cooperation with an NCIMS task force, is developing a needs assessment for the data base and planned to issue a request for contract proposals by the end of July 1992 and award the contract by the end of fiscal year 1992. FDA officials estimate that the data base will become operational sometime in fiscal year 1993. Developing and implementing the national data base will be important to the success of

FDA and state monitoring of milk safety, especially in light of the revisions to the Milk Ordinance.

In some cases FDA's procedures are not specific enough to evaluate the agency's accountability for the program. FDA's existing guidance on how it will determine the animal drugs for which the states and industry must test does not provide clear criteria for how and when FDA will make this decision. As of May 1992 CVM had not specified any drugs for which the states and industry must test in addition to four beta lactams because, according to CVM officials, FDA had not yet gathered sufficient information to make this determination. Without specific criteria and procedures for designating additional drugs, it is not possible to determine what additional information CVM is waiting to receive.

In still other cases FDA has proceeded without fully planning its actions or analyzing the implications of those actions and decisions. For example, in January 1992 FDA told industry to begin testing for four approved beta lactam drugs, although there were no available test methods at the time that could detect all four drugs at their tolerance and/or safe levels. In March 1992 FDA recommended that industry could use any of the officially recognized methods that could detect at least four of six beta lactam drugs at their tolerance and/or safe levels.

Limitations in and Lack of Agreement on Test Methods Complicate Monitoring Efforts

Limitations in existing testing technology is the primary deterrent to bridging the gap between drug usage and testing. Successfully implementing the revisions to the Milk Ordinance and improving milk monitoring depend on FDA's success in overcoming this deterrent. Yet, FDA does not agree with the states and the dairy industry on the type, accuracy, and precision of the test methods needed to take regulatory action under the Milk Ordinance. In particular, CVM officials believe that regulatory methods, which are time consuming to develop and operate and require specialized equipment, are needed to identify and measure specific drugs in milk to take regulatory action. On the other hand, the states and industry want to use more rapid and less sophisticated methods to screen milk under the Milk Ordinance. Consequently, although FDA has made some progress developing regulatory methods, controversy remains over the methods needed for monitoring milk. Until this controversy is resolved, progress in implementing the revisions to the Milk Ordinance and improving federal and state oversight of industry safety efforts will be limited.

Overview of Testing Methods

Because of limitations in existing technology, no single test method or procedure can detect or quantify all animal drug residues that may be present in milk. Therefore, FDA and the states cannot routinely test milk for all drug residues that may be present. However, several types of existing methods claim to detect the presence of certain animal drug residues in milk. These test methods can be grouped into two general categories: regulatory methods and screening methods, each of which has certain uses and limitations.

As part of the new animal drug approval process (see ch. 1), animal drug manufacturers must submit an analytical method to FDA that is capable of reliably detecting and measuring residues of the drug at the tolerance level in/on the food product, such as milk, derived from the animal for which the drug approval is being sought. These methods, called regulatory methods, must be validated under formal FDA laboratory procedures before FDA approves the drug. FDA requires regulatory methods to measure how much of a specific drug is present in milk or meat to determine whether residues of the drug exceed permitted levels.

Usually a regulatory method consists of two testing procedures: a determinative procedure and a confirmatory procedure. The determinative procedure is used to quantify or measure the amount of a drug residue present in milk. Because this procedure is not always able to specifically identify the drug being tested, the confirmatory procedure is used to verify the specific identity of the drug. Thus, regulatory methods can consist of one or more testing procedures—typically chemical-based analysis of some type—such as high-pressure liquid chromatography, thin layer chromatography, gas chromatography, and mass spectrometry. CVM officials consider the more costly and difficult mass spectrometry testing to be the most reliable confirmation method for identifying specific drug residues for enforcement purposes.

Because drug companies do not have to submit a method to FDA for unapproved uses of their drugs, the federal government usually bears the burden of developing the regulatory methods needed to detect and measure illegal residues and pursue enforcement action. In addition, sponsor-submitted regulatory methods are generally single-residue methods because they are intended to identify and measure specific drug residues. For enforcement purposes, FDA prefers to develop and use multiresidue methods that are capable of efficiently detecting and identifying, from a single test, more than one compound having similar chemical and physical properties.

Responding to the dairy and food industries' demands for rapid, inexpensive test methods to screen billions of gallons of milk products for several drug residues, the diagnostics industry has developed several screening methods, also commonly called rapid screening test kits. According to FDA, these tests are technically uncomplicated analytical methods that can respond in a relatively short time to the presence of drug residues above certain levels in milk or other animal products. Screening methods may be either multiresidue or single residue, depending on the design of the method. Generally, regulatory methods differ from screening methods in that the former use more complex technology and are typically more time consuming, difficult, and costly to run, but yield more definitive information about the identity and quantity of a drug residue.

Unresolved Differences in the Type of Methods Needed for Monitoring Milk

CVM officials and others are concerned about the accuracy, precision, reliability, and use of screening methods. In particular, performance is suspected to vary widely among test kits and even within kits that claim to detect multiple drug residues. CVM officials are concerned about whether commercially available screening methods (1) may fail to indicate the presence of a drug residue that is actually present in milk (false negative); (2) may indicate the presence of a drug residue that is not present in milk (false positive); or (3) may indicate the presence of a drug residue that is present in milk, but at or below FDA's tolerance and/or safe level for the drug (false violative). According to CVM officials, screening methods that produce false negative results may fail to protect public health, and false positive and false violative test results may be economically detrimental to the dairy industry and ultimately costly to the consumer. Other concerns include whether screening methods can perform consistently in the hands of nontechnical users and whether multiple compounds, permitted levels of bacteria, or components in the milk itself may adversely affect the performance of the methods.

Moreover, screening methods are typically qualitative in nature—they often simply produce a positive or negative response depending on whether a residue is detected, but generally they cannot identify the specific drug residue or the amount that may be present. For example, a multiresidue rapid screening test kit may tell a user that a sulfonamide may be present, but not which one(s) or at what amount(s). CVM officials believe that screening test methods can be used to determine quickly and economically that the milk tested does not contain a drug residue within the limits of the particular test used. However, CVM officials believe that screening tests provide only an indication that milk tested may contain a

drug residue, but not necessarily one that is illegal or poses a health risk. Therefore, as a matter of policy, CVM requires further testing with regulatory methods to confirm a positive screening test result to determine conclusively whether a specific drug residue exceeds permitted levels in milk in order to take regulatory action and withstand possible challenges in court. However, FDA has not taken any enforcement action on the basis of its regulatory methods for animal drugs in milk because, under the Milk Ordinance, this responsibility lies with the states. On occasion, FDA has confirmed testing results using regulatory methods upon request from the states.

In contrast, under the revised Milk Ordinance, the states and the dairy industry may take action on the basis of positive screening method results without confirming the results with FDA regulatory methods. According to the memorandum of understanding between the NCIMS and FDA, the states are responsible for taking initial enforcement actions for Grade A milk. Under the revised Milk Ordinance, the states can take these actions on the basis of positive results from AOAC Research Institute-evaluated and FDA-accepted screening methods that are verified by the same or a similar screening method. In addition, the dairy industry, which is testing every tanker of milk with screening methods for selected beta lactams, may reject loads of milk on the basis of screening test results.[1]

FDA has not resolved the discrepancy in evidentiary standards for pursuing regulatory action on the basis of residue violations with those of the states and industry under the Milk Ordinance. The Director, Office of Science, acknowledged that the states may not need to use regulatory methods, such as mass spectrometry, to confirm positive screening test results under the Milk Ordinance. Resolving the discrepancy in scientific and regulatory standards between CVM and the states and industry on appropriate test methods and procedures for monitoring animal drug residues in milk has become even more important because of the recent revisions to the Milk Ordinance. CVM officials have stated that they will identify additional problem animal drugs for the states and industry to test for even if FDA does not have a test method to confirm multiresidue screening test results. However, as noted earlier, FDA has not yet specified any drugs that the states and industry must test for in addition to the

[1]Under the revised Milk Ordinance, until AOAC evaluates and FDA accepts new screening methods, the dairy industry is not required to confirm the results of positive screening methods used to screen for beta lactam drugs with regulatory methods. According to FDA's guidance, if industry chooses to confirm positive screening test results, FDA recommended that screening methods officially accepted under the revised Milk Ordinance, including the disk assay, be used for "confirmation" purposes. If the confirmatory test is negative, the results of the confirmatory test supersede the initial test result.

selected beta lactams using the four officially sanctioned screening methods under the revised Milk Ordinance. Although these methods have not yet been evaluated under the AOAC Research Institute/FDA program, information from the manufacturers of the methods and others indicate that these methods can detect about 36 of the 82 animal drugs known to be or suspected of being used on dairy cows at or below the tolerance/safe level for these drugs, depending on how the tests are calibrated and conducted. CVM will determine how and which screening test methods will eventually be used under the revised Milk Ordinance after the methods have been evaluated as part of the AOAC Research Institute/FDA program discussed earlier.

In addition, pursuing regulatory action with a regulatory method may be unnecessary to deter drug misuse on dairy cows. According to a California state milk control official, dairy farmers are keenly aware of at least one rapid screening test's capability to detect certain sulfonamides. At the risk of financial loss from a positive test result, dairy farmers are abstaining from using sulfonamides, according to this official. Moreover, the dairy industry already uses the results of certain screening methods for several drug residues, including sulfonamides and tetracyclines, and rejects tankers of milk for processing that test positive, according to a representative from the milk processors industry.

CVM officials are, however, concerned that a significant amount of Grade A milk that FDA considers safe for human consumption may be unnecessarily discarded because of high false-positive and false-violative results from certain rapid screening test kits. CVM officials believe that although the dairy industry has been willing to accept the results of screening tests under the revised Milk Ordinance for selected beta lactam drugs, the industry may be less willing to accept the results of these methods for other possible drug residues because of problems with false-positive and false-violative results. Therefore, CVM officials believe that the results obtained with these screening methods must be evaluated against the results of the more technically complex regulatory methods to determine whether the test kits perform within acceptable parameters. However, according to a representative from the milk processing industry, FDA should let the dairy industry worry about the economics of dumping milk that may only be potentially contaminated.

Since 1987 CVM has planned to develop and/or improve and validate regulatory methods and procedures to identify and quantify the presence of 48 drugs in milk on the basis of a priority scheme. CVM ranked each

drug—on the basis of suspected approved and unapproved use on dairy cows and possible human health risks from potential residues in milk—to develop and validate regulatory methods. As of June 1992 FDA had developed and validated regulatory methods to test for residues in milk of three unapproved animal drugs: ivermectin, clorsulon, and sulfamethazine. In addition, FDA had developed regulatory methods to test for 20 other animal drugs, but because of resource constraints, the methods had not yet been validated. Regulatory methods for the remaining 25 drugs on FDA's priority list are in various stages of development. In fiscal year 1992 CVM budgeted about $1.5 million to develop and validate methods to test for animal drug residues in milk and meat tissue but could not estimate the portion devoted to milk tests because of the way program expenditures are accounted for.

CVM does not know when it will complete development and validation of the planned test methods and has not fully estimated the costs of development and validation. According to CVM officials, it takes, on average, about 12 to 18 months to develop and validate an individual method. However, in some cases, it is not possible to reliably estimate when a regulatory method will be developed and validated because of limits in science, technology, and resources, according to the Special Assistant to the CVM Science Director. For example, FDA officials have been trying to develop a confirmatory procedure for approved beta lactams for 5 years.

Despite CVM's efforts, however, state, industry, and CFSAN Milk Safety Branch officials have criticized CVM's development of regulatory test methods that are not practical for the states to use and that may go beyond their testing needs under the Milk Ordinance. For example, although some states have the capability and are using regulatory methods to detect and confirm drug residues in milk, many states lack the necessary laboratory facilities, personnel, and resources to use the regulatory methods that FDA's Denver lab is using for the CVM monitoring program or that CVM is developing. According to state and industry officials, screening methods would be more useful to them than the regulatory test methods that CVM is currently developing. Screening test methods provide the states and industry a means to screen economically and efficiently large quantities of milk for a wide range of animal drug residues. In a July 1990 memorandum to the CVM's Director of the Office of Science, the Chief of the Milk Safety Branch concluded that, "unless we [FDA] can provide the states with analytical methods that are practical for them to use with their current budgets, we are wasting FDA's resources." In February 1991 the NCIMS

Chairman stated that FDA needs to take a leadership position in developing and validating rapid screening test methods for the states and industry to use.

According to CVM officials, although everyone wants screening methods to detect a wide variety of drug residues in milk which are reliable, quick, inexpensive, and simple to run under various use conditions, existing technology is unable to meet this demand. CVM officials are concerned that some state and industry officials are not aware of the limitations in screening methods noted above and existing testing technology. For example, for several years industry and state officials believed that the disk assay, a screening method, was capable of detecting several antibiotics in milk. However, this method is able to detect only four drugs at their tolerance and/or safe levels. CVM officials believe that regulatory methods are needed as a standard or reference against which to evaluate the performance of a screening method as well as to confirm positive results obtained from these methods.

According to CVM's Director of Science, CVM is not developing rapid screening test kits because (1) several manufacturers are producing test kits and are generally faster than the federal government in developing and marketing new and improved versions and (2) CVM should oversee and not compete with this industry. In addition, these methods generally cannot be used to sustain an FDA regulatory action, according to the Director.

Under FDA's approach, the agency basically assumes that milk is not contaminated unless the residues of an individual animal drug are detected and confirmed to be present at or above permitted levels. While this approach is a traditional strategy for successful action against individual violations of allowable residues, it does not ensure that milk is free of contaminants that were not tested for or are not permitted but nonetheless are present below safe levels. There will always be a need for FDA and the states to monitor the safety of the nation's milk supply. However, the need for such efforts could be reduced if there were assurances that the dairy industry itself was taking all possible steps to ensure that the milk supply is free of contaminants, especially since neither FDA nor the states have the resources to test all milk produced in the United States. To their credit, the dairy industry and veterinarians have been working to improve animal husbandry practices and responsible animal drug use on dairy farms. In addition, as noted earlier, the dairy industry is testing over twice the number of milk samples as FDA and the states for several drug residues in addition to the four beta lactams

currently required under the Milk Ordinance. However, FDA's regulatory approach to monitoring drug residues does not provide the level of verification necessary for consumers to trust industry efforts to build safety assurances into the milk supply. If consumers are uncertain about the risks of animal drugs in their milk because they perceive a breakdown in milk monitoring, they may decrease their consumption of milk products, regardless of the actual health risk imposed by residues in milk. Reduced demand for milk products could cause economic harm to milk producers and processors as well as adverse health consequences to consumers who depend on milk as a primary source of calcium in their diets.

Finally, CVM plans to develop and validate single-residue regulatory methods to update methods that animal drug manufacturers had submitted for 10 previously approved dairy cow drugs. According to the Director of the Office of Science, the original regulatory methods to detect residues of these drugs were developed before the mid-1970s, when test methods were not as sophisticated as the chemical-based methods that FDA now requires. FDA could try to compel the manufacturers to submit updated methods if the agency shows that the existing methods are no longer adequate for detecting residues. On the basis of past experience, agency officials pointed out that this is potentially so time consuming and resource intensive—primarily because of the administrative hearing and appeal process—that it is more efficient and cost effective for the agency to develop the test methods and validation data itself. However, FDA has not analyzed the costs and benefits of updating older methods rather than pursuing legal action to compel manufacturers to update their older methods. In addition, officials from the Animal Health Institute, which represents drug companies, question whether FDA needs to update methods that, while time consuming, may be satisfactory for regulatory purposes, especially since FDA has not taken any enforcement action on the basis of its regulatory methods for residues in milk.

FDA's New Monitoring Program Does Not Provide Conclusive Information

In February 1991 CVM started the National Drug Residue Milk Monitoring Program to assist and supplement residue testing efforts under the Milk Ordinance. According to FDA's guidance, the CVM monitoring program was designed to provide (1) an indication of animal drug residues that may be present in milk; (2) an indication, through follow-up investigations, of the extent that farmers, distributors, and veterinarians comply with federal regulations on the proper use of drugs on dairy cows; and (3) information on drug residues in milk for federal, state, and local milk officials to design

educational and enforcement programs. However, limitations in the program's sampling, estimation procedures, and testing preclude drawing any statistically valid conclusions about the presence or absence of animal drug residues in the nation's milk supply and raises questions about the benefits the program is able to provide in adding assurance about the safety of the nation's milk supply.

During the first year of the program, which cost about $270,000, state milk control officials, in cooperation with FDA regional milk specialists, collected on average 5 raw milk samples a week nationwide from selected milk processing plants—about 250 samples in total.[2]

Initially, FDA's Denver District Laboratory tested the samples for 11 animal drugs (8 sulfa drugs and 3 tetracycline drugs) and began testing for a 12th drug, chloramphenicol, in June 1991. Nine of these 12 drugs are unapproved for use in dairy cows. According to the Director of the Office of Surveillance and Compliance, CVM selected these 12 drugs for testing on the basis of information gathered from multiple sources on suspected animal drug usage and the agency's ability to test for these drugs. CVM expanded the program in 1992 to increase the yearly sample size from 250 to 500[3] and the number of methods used to test for five additional drugs (four beta lactams and novobiocin, an antibiotic drug used to treat mastitis).[4] The expanded program will cost about $500,000 in fiscal year 1992. As of May 1992 the Denver laboratory had confirmed the presence of five sulfa drug residues in milk samples tested (one sulfadimethoxine and four sulfamethazines), but the residues were all below the tolerance or safe levels established by FDA.

However, no conclusion can be drawn from these test results. The few samples taken each week at the dairy plants were not randomly selected within a given plant and did not account for differences in milk volume processed at individual dairy plants or for seasonal and regional variations in possible drug usage. Furthermore, according to FDA officials, some dairy plants, and therefore farmers, may have learned in advance about the weekly sites selected for testing. Knowing in advance which sites were to be selected each week may have allowed plants and farmers to withhold any milk that might possibly have contained drug residues on the day of

[2]About 225 samples were Grade A milk and 25 samples were non-Grade-A milk.

[3]210 samples of Grade A milk and 290 samples of non-Grade-A milk.

[4]FDA program guidance did not specify specific beta lactams to be tested but, as noted above, the disk assay can detect four beta lactams at their tolerance and/or safe level. In addition, FDA does not have a method to confirm positive novobiocin results at this time.

the test. To reduce potential bias, recent changes to program procedures reduce the amount of advance notification time to the sites selected. The program also tested for only 12 of the 82 drugs that we identified are known to be or are suspected of being used on dairy cows and that may leave residues in milk (see ch. 2).

FDA has not yet resolved the relationship between the CVM monitoring program and residue testing conducted by the states and the dairy industry under the revised Milk Ordinance. For example, the CVM monitoring program began using the disk assay to test milk samples for beta lactams in March 1992. However, the states have been using the disk assay since 1980 to test millions of milk samples and, under the revised Milk Ordinance, industry was required to test every tanker of milk for these same drugs. Expanding the CVM monitoring program to use the disk assay would not likely provide FDA and the states with data as useful to them as those they could obtain from collecting existing test data via the proposed national residue data base.

FDA officials agree that the statistical limitations in the program preclude drawing any valid conclusions about the incidence of animal drug residues in the nation's milk supply. However, FDA officials believe that, given existing resource constraints, the program can provide an indication of whether animal drug residues are present in the milk. According to CVM's Director of Surveillance and Compliance, unlike other surveys of animal drug residues in milk, which were also not statistically projectable, the CVM monitoring program uses the best analytical methods available to detect and confirm the presence of residues. In addition, the Director said that the program is still evolving and FDA may change the program objectives when the revisions to the Milk Ordinance are implemented. For example, FDA is considering whether to use the program to audit state and industry testing in the future. In addition to monitoring milk, FDA's Denver laboratory also provides a resource for developing and validating test methods, demonstrating and training state officials in the use of test methods, and confirming the results of state tests upon request, according to an FDA official.

Conclusions

Despite recent initiatives, FDA and the states have made limited progress in monitoring milk to ensure that the nation's milk supply is free of illegal and/or potentially unsafe animal drug residues. Implementing the 1991 revisions to the Milk Ordinance to improve drug monitoring has proven difficult to achieve, and the outcome of the new joint AOAC Research

Institute/FDA program to evaluate and recommend screening methods for use under the Milk Ordinance is uncertain. However, lack of a clear FDA action plan has created unnecessary frustration and confusion for industry and the states and delayed progress. The dairy industry and others have been working to build greater assurances of safety into the nation's milk supply, including testing for more drug residues than FDA and the states. However, limitations in federal and state oversight of industry efforts, especially validation of screening methods and verification of industry test results, could impair consumer confidence in the safety of the nation's milk supply.

Although limitations in existing technology complicate monitoring efforts and present a hurdle for implementing change, FDA has not yet resolved the type of test methods and procedures that the states and industry may be able to use under the Milk Ordinance to deter illegal and/or potentially unsafe animal drug residues in milk. FDA has made some progress developing sophisticated methods to take regulatory actions. However, the development of these methods has been controversial because they are not practical for the states to rapidly screen milk and may go beyond what the states need to take regulatory action under the Milk Ordinance. In addition, in a time of limited resources, FDA's plans to update regulatory methods submitted by drug manufacturers as part of previous drug approvals—rather than try to compel the manufacturers to update their methods—appear questionable because FDA has not conducted a cost/benefit analysis of this approach, including the long-term implications of further improvements in testing technology that may require older methods to be updated.

Furthermore, the utility of FDA's $500,000 effort to test a limited number of samples is highly doubtful, especially considering the anticipated increased monitoring efforts by the states and industry under the revised Milk Ordinance and the lack of resources for other needs, like the national residue data base and test method validation, that need to be done to meet the requirements of the revised Milk Ordinance.

Overall, FDA lacks a comprehensive strategy for monitoring animal drugs in milk that integrates the multiple players involved; defines roles and responsibilities; outlines the optimum sampling and testing scheme to deter drug misuse, considering limited federal and state resources; and provides for resolution of issues surrounding testing methods that the states and industry may use under the Milk Ordinance. FDA's recently

formed Milk Work Group is a good start, but a comprehensive strategy is still lacking.

Recommendations

To better ensure the safety of the nation's milk supply, we recommend that the Commissioner, FDA, develop a comprehensive strategy to monitor milk for animal drugs that optimizes state and industry testing under the Milk Ordinance, outlines FDA offices' roles and responsibilities, and integrates the various efforts to improve milk monitoring. The strategy should, at a minimum, include

- developing an FDA action plan to implement the 1991 revisions to the Milk Ordinance, focusing on those drugs that pose the greatest threat to the safety of the nation's milk supply;
- resolving which types of test methods and what level of precision are necessary for the states and industry to use under the Milk Ordinance;
- conducting a cost/benefit analysis of FDA's updating older regulatory methods rather than trying to compel drug manufacturers to update their older methods; and
- reexamining the objectives and mission of FDA's monitoring program to determine (1) its relationship to state and industry testing under the Milk Ordinance and (2) the costs and benefits of this program versus increased funding for other efforts needed to implement the revisions to the Milk Ordinance.

Limited Enforcement of Extra-Label Uses Undermines Controls Over Animal Drugs

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), an animal drug must be used in accordance with the label approved by FDA. Use of the drug other than as specified on the approved label is considered an extra-label use and is a violation of FFDCA. Despite this restriction, FDA's Center for Veterinary Medicine (CVM) has established a policy under which FDA will ordinarily not pursue enforcement action when a veterinarian violates the law by treating a food-producing animal with a drug in an extra-label manner, if the animal's life is in danger and certain conditions are followed.

Although FDA officials intended that extra-label uses under the policy would occur in rare circumstances, evidence indicates that veterinarians are routinely using and prescribing drugs in an extra-label manner for dairy cows. Furthermore, federal and state regulators generally cannot ensure that the conditions of the extra-label use policy are followed because they (1) cannot detect residues of drugs in milk resulting from most extra-label uses on dairy cows and (2) lack sufficient information on whether veterinarians are adhering to policy requirements. Veterinarians and CVM officials contend that extra-label use is necessary because the number of animal drugs approved to treat dairy cows is insufficient and many of the approved dosages for animal drugs are no longer effective. However, FDA's limited enforcement of extra-label uses undermines controls over drugs used on food animals. In addition, it may discourage animal drug companies from seeking FDA approval of those uses of their drugs that are now extra-label uses. Recent proposals by officials from FDA, consumer groups, the Animal Health Institute (AHI), and the American Veterinary Medical Association (AVMA) to address extra-label use problems and CVM's policy all have limitations because of the persistent lack of data on the need for extra-label drug use on food-producing animals and whether veterinarians have sufficient information to make informed decisions on the efficacy and safety of such uses.

Policy Describes Conditions When FDA Will Generally Not Enforce Drug Violations

Under CVM's extra-label use policy,[1] veterinarians may treat food-producing animals with drugs not approved for them, and/or not approved for the particular manner in which used, if the animal's health is otherwise immediately threatened or suffering and/or death would result from not treating the affected animal. According to CVM's policy, FDA will ordinarily refrain from taking enforcement action against licensed veterinarians for

[1]Compliance Policy Guide 7125.06, "Extra-Label Use of New Animal Drugs in Food-Producing Animals."

using or prescribing any drugs they can legally obtain, provided the veterinarian

- makes a careful medical diagnosis within the context of a valid veterinarian/client/patient relationship (see app. II);
- determines that (a) there is no approved drug specifically labeled to treat the condition diagnosed or (b) treatment with an approved drug at the recommended dosage has been ineffective;
- establishes procedures to ensure that the identity of the treated animals is carefully maintained; and
- significantly extends the time period for drug withdrawal before marketing meat, milk, or eggs from the treated animals; and takes measures to ensure that the assigned time periods are met and no illegal residues occur.

The conditions of CVM's policy do not permit nonveterinarians, such as dairy farmers, to treat food-producing animals with drugs not approved for them and/or in an unapproved manner. In addition, CVM has declared that certain drugs may not be used at all under the extra-label use policy because of public health concerns. For example, CVM has banned the use of chloramphenicol and sulfamethazine and the extra-label use of nitrofurazone to treat dairy cows because residues of these drugs in milk pose an unacceptable risk to humans. Furthermore, CVM's policy applies only to drugs used for therapeutic purposes and does not apply to drugs used for production purposes, such as for weight gain or for routine disease prevention.

Under CVM's policy veterinarians can use an approved animal drug on a species or for a condition not listed on the label, by a different route of administration, or at higher dosage levels than those stated on the label. For example, a veterinarian could use or prescribe a drug approved for use only on pigs to treat a dairy cow. Because FFDCA prohibits any unapproved use of a new animal drug, an extra-label use is still a violation of the law. However, under CVM's policy FDA is unlikely to take enforcement action provided a licensed veterinarian follows all the conditions listed above. CVM officials said that the intent of the policy was to recognize the need, in special circumstances, for veterinarians to use animal drugs in unapproved ways, yet still protect public health by providing guidelines to the veterinarian for using the drugs. CVM officials believe that the policy is a reasonable exercise of its discretionary authority not to take enforcement action in certain circumstances. In addition, these officials believe that extra-label drug use should be a rare occurrence because the policy's criteria are restrictive.

CVM established the extra-label use policy in 1984, in cooperation with the AVMA and others, to address what CVM officials characterized as a situation in which the illegal use of animal drugs was out of control. Before the current policy, CVM allowed veterinarians to use or prescribe any drugs they could legally obtain as long as illegal residues did not occur. However, CVM officials determined that veterinarians and producers were misusing a wide range of animal drugs on food-producing animals, including many drugs that were not approved by FDA for any use. CVM officials realized that they could not pursue every violation of the law and developed the extra-label use policy, in part, to help set priorities for enforcement actions.

Extra-Label Drug Use Is Routine

As noted in chapter 2, FDA does not know the extent to which animal drugs are illegally used on dairy cows. However, evidence from private veterinarians, AVMA officials, and others indicates that extra-label drug use on dairy cows is a routine practice, contrary to CVM's intentions that such use occur only in special circumstances. In 1985 congressional hearings shortly after the extra-label use policy was instituted, CVM's Director stated that CVM did not expect extra-label use to be routine and had instituted the policy to allow for emergency unapproved uses in the best interest of animal and human health. However, according to FDA and AVMA officials, extra-label use is routine because of the limited range of animal drugs approved for use on dairy cows and because the dosage levels at which some drugs are approved are ineffective. According to several veterinarians who treat dairy cows, 40 to 85 percent of their drug prescriptions for dairy cows are extra-label use prescriptions. AVMA officials confirmed that while they have not collected data on how frequently veterinarians use the policy, a significant number of veterinarians' prescriptions for dairy cows are extra-label uses. Veterinarians and FDA and AVMA officials stated that few drugs are approved at dosages high enough to treat some common illnesses that afflict dairy cows, such as mastitis. Therefore, veterinarians use and prescribe stronger, more effective dosages under the extra-label use policy. In addition, despite the policy restrictions, some veterinarians choose to use drugs not approved for dairy cows to treat certain diseases because they consider them to be more effective or less costly than drugs approved for these same uses on dairy cows. For example, AVMA officials told us that although several anesthetics, analgesics, and sedatives are approved for use in dairy cows, some veterinarians prefer to use other drugs not approved for dairy cows because they are more effective.

FDA officials have been aware for several years that veterinarians routinely use unapproved drugs and approved drugs in an unapproved manner to treat dairy cows. For example, an FDA-sponsored survey in Colorado in 1985 found evidence of possible extra-label use on nearly 50 percent of the dairy farms inspected. Another drug survey in Illinois in 1988 found over 200 different animal drug products on the dairy farms inspected; 58 percent of these products were not approved for use on dairy cows. Finally, data from FDA check ratings—inspections of selected dairy farms to validate state inspection programs—in 1990 and 1991 indicated that 62 animal drugs not approved for use on dairy cows were found on dairy farms across the nation; 42 drugs were not approved for use in any food-producing animal. CVM's Deputy Director told us that FDA knows that extra-label use is very extensive.

Limited Enforcement of Extra-Label Uses Undermines Controls Over Animal Drugs

Limited enforcement of extra-label uses effectively undermines controls over animal drugs used on dairy cows. When a drug is used in an extra-label manner, important safeguards against marketing unsafe animal drugs are bypassed and health and safety data that FDA usually requires for approving drugs will likely be missing. Veterinarians' decisions on using drugs in an extra-label manner may be made in the absence of data on how the drug works in a dairy cow. Moreover, FDA generally cannot ensure that the conditions of the policy are followed by veterinarians because neither FDA nor the states can detect residues of many drugs used in an extra-label manner under the policy. In addition, FDA does not routinely monitor veterinarians' extra-label uses under the policy. Veterinarians' routine practice of treating dairy cows in an extra-label manner and FDA's inability to ensure that the conditions of the policy are followed may discourage animal drug manufacturers from seeking approval of additional uses of their animal drugs because they can sell the drugs without incurring additional regulatory cost or enforcement action.

Important Health and Safety Data May Be Lacking

Under FFDCA, animal drug companies are required to provide adequate data to FDA before marketing the drugs to demonstrate that their drugs are safe and effective for each use and species of animal for which the drugs are intended. In addition, if the drugs are intended for use in food-producing animals, the companies must provide data showing that food products derived from treated animals are safe for human consumption (see ch. 1). However, when an animal drug is used in an extra-label manner, neither FDA nor the animal drug companies have performed the studies necessary to show that the drug use is effective and safe for animals, people, and the

environment. Furthermore, analytical methods are generally not available to detect residues of drugs not approved in food-producing animals or used in an unapproved manner. Consequently, public health is at an increased risk because consumers may be exposed to residues in their food that have not been shown to be safe and that probably escape detection.

Under the policy, the approximately 40,000 veterinarians in the United States rely on available information and their best judgment and experience in place of FDA premarket approvals and data on drug efficacy, animal safety, and human safety to make extra-label use decisions. However, veterinarians may lack adequate information on the dosage levels and withdrawal periods (e.g., milk discard times) needed to ensure that illegal and/or unsafe residues do not occur in food products, such as milk, from treated animals. According to a veterinarian's guide to safe animal drug use prepared by the AVMA and the National Milk Producers Federation, it is extremely difficult to provide accurate withholding periods for drugs used in an extra-label manner. Veterinarians can obtain some information on extra-label uses through the Food Animal Residue Avoidance Databank,[2] but drug safety information based on the FDA drug approval process, including a tolerance and/or safe level and a withdrawal period, may still be lacking. For example, one manufacturer, concerned about the reported extra-label use of its product, sent letters to over 7,000 dairy veterinarians advising them about the proper use of its drug approved for dairy cows, informing them that no safety data are available for the drug when it is administered to dairy cows in an extra-label manner, and warning them that illegal residues may result from such extra-label use.

The potential lack of information is of particular concern when extra-label use involves a drug not approved for use on any food-producing animal. In such cases, the drug company is not required to submit any information to FDA on potential health risks to humans from consuming food containing residues of the drug. For example, under the policy veterinarians may use flunixin, an analgesic and anti-inflammatory drug, on dairy cows even though the drug is approved for use only in horses not intended for food. FDA has not established a tolerance for flunixin residues in milk or a milk discard time for use of the drug on dairy cows. CVM officials stated that

[2]The Food Animal Residue Avoidance Databank is a USDA-sponsored program at the University of Florida designed to provide veterinarians with information on how to avoid drug residues in food when prescribing animal drugs in an extra-label manner. Veterinarians may call the data bank for information free of charge. USDA is responsible for monitoring animal drug residues in meat and poultry.

because flunixin is not approved for use on dairy cows, the drug company has not submitted information on the potential toxicity to humans of flunixin residues in milk or on an appropriate milk discard time for dairy cows. However, on the basis of general surveillance data, FDA officials believe that flunixin is commonly used on dairy cows. Flunixin was found on dairy farms in five of six FDA regions during FDA check-rating inspections in 1990 and 1991.

When extra-label use involves animal drugs already approved on at least one food-producing animal, adequate safety information may still be lacking because different animals may process drugs into different compounds (metabolites), which can pose concerns of their own. According to FDA, animal drug metabolites are likely to present health risks that may be as important as residues from the parent drug because of their amount, persistence, or potential for toxicity. For example, according to FDA data, several of the metabolites that develop from sulfamethazine, a drug banned by FDA for use in dairy cows, may present cancer risks similar to those associated with sulfamethazine itself. Furthermore, many animal drugs were approved years ago on the basis of health and safety data that would not be considered acceptable today to support the approval of a new animal drug use because of advances in science and improvements in testing procedures. Consequently, FDA may not have sufficient safety information on an animal drug to support the increased risks to consumers resulting from exposures of the drug via extra-label uses.

Equally important, for many drugs used under the extra-label use policy, such as flunixin, not only are the proper withdrawal data limited, but no analytical method exists to detect residues of the drug in milk. One of the conditions for extra-label use under CVM's policy is that the veterinarian must ensure that no illegal residues occur. However, because reliable methods to detect possible animal drug residues generally do not exist, as explained in chapter 3, milk cannot be tested to ensure that illegal residues are not present.

FDA Generally Cannot Ensure Policy Conditions Are Followed

FDA generally cannot ensure that the conditions of the policy are followed by veterinarians. The same reasons that make it difficult for FDA to take enforcement action against illegal drug uses make it difficult for FDA to take enforcement action against extra-label uses under the policy. Specifically, federal and state regulators lack acceptable test methods to detect the residues of many drugs used in an extra-label manner, preventing FDA from providing assurance that illegal and potentially

harmful animal drugs residues are not contaminating the nation's milk supply. In addition, FDA cannot ensure that veterinarians are adhering to the policy's conditions because FDA does not routinely monitor the use of the policy by veterinarians.

Drug manufacturers, when seeking approval for an animal drug in a food-producing animal, must submit to FDA a method for detecting residues of the drug only in the tissue or edible product (e.g., milk) of the species for which the drug is intended. They are not required to submit detection methods for potential extra-label uses of their drugs. Thus, FDA and state regulators generally lack methods to detect residues from drugs used in an extra-label manner. For example, as noted above, evidence suggests that veterinarians are using flunixin in an extra-label manner to treat dairy cows. However, because the drug was never approved for use in dairy cows, the drug manufacturer was not required to submit a method to detect flunixin residues in milk, and neither FDA nor state regulators have a method to detect residues of flunixin in milk.

Even when CVM has determined that a drug may not be used in an extra-label manner under the policy, it may not be able to enforce this ban because it lacks a method to detect residues of the drug in milk. For example, in 1991 FDA banned extra-label use of nitrofurazone on dairy cows and other food animals because, among other things, it is a suspected carcinogen. As noted in chapter 2, FDA and state officials believe that nitrofurazone was being used in an extra-label manner on dairy cows. However, neither FDA nor the states have any acceptable method to detect nitrofurazone in milk.

CVM's extra-label use policy provides for possible enforcement action against anyone who uses animal drugs in an unapproved manner, even if no residues are detected. However, without the ability to detect residues in milk from the extra-label use of animal drugs on dairy cows, FDA generally cannot enforce the policy. According to a recent CVM task force report on the enforcement of extra-label uses,

> . . . regulatory actions based solely on the extra-label use of drugs, in the absence of the detection of illegal tissue residues, have been extremely rare. Enforcement actions against individuals responsible for the unapproved use of drugs are difficult to document with evidence unless a residue has occurred in food. Without residues, there is ordinarily no direct evidence of extra-label use.

For example, in 1991 FDA decided not to take enforcement action against a veterinarian for not complying with the extra-label use policy because the agency lacked an adequate method to detect residues of tysolin in milk. According to the Director of CVM's Office of Compliance, although CVM's policy states that detection of a drug residue is not a prerequisite for taking action against a veterinarian for violating the policy's conditions, the Department of Justice, to whom FDA must refer criminal prosecution cases, usually will not prosecute a case unless it involves illegal residues or animal death as the result of the veterinarian's actions.

Furthermore, when FDA learns about illegal residues, the agency typically sends regulatory or warning letters to the offending party. According to CVM officials, resource constraints (too few investigators), insufficiently trained investigators, and legal obstacles hinder FDA enforcement actions. Although illegal drug residues are a priority concern to CVM, FDA and the states have been able to conduct follow-up investigations on only about 20 percent of the illegal drug residue cases reported from the USDA because of resource constraints, according to CVM officials. A recent CVM task force on extra-label uses recommended, among other things, establishing a coordinating group of representatives from FDA's CVM, Office of Regulatory Affairs, and Office of General Counsel; USDA; and the Department of Justice to overcome the current obstacles in bringing effective enforcement actions in tissue residue cases. Although CVM's Director agreed with the recommendation, he is not optimistic that CVM will receive the additional funding to significantly increase both the number and training of investigators as recommended by the task force.

FDA's lack of authority to issue civil penalties (i.e., monetary fines) is one legal obstacle that may be hindering efficient enforcement of illegal animal drug residues. Under FFDCA, FDA can pursue criminal prosecutions for violations of the act but cannot issue civil penalties. However, because of the resource- and time-consuming nature of criminal prosecutions, FDA has been selective in seeking prosecutions for illegal animal drug residues. We have reported in the past that civil penalty authority would provide FDA with an additional deterrent to protect the public from being exposed to illegal chemical residues.[3] Although several bills have been introduced in the current Congress to provide civil penalty authority to FDA, the administration has not supported them. Another legal obstacle involves FDA's difficulty in proving that the person being investigated delivered adulterated food into interstate commerce in order to establish

[3]Pesticides: Need to Enhance FDA's Ability to Protect the Public From Illegal Residues (GAO/RCED-87-7, Oct. 27, 1986).

jurisdiction under FFDCA. This issue is also addressed in pending legislation.

FDA is also unable to ensure that veterinarians are using and prescribing animal drugs within the guidelines of the extra-label use policy because FDA does not generally monitor veterinarians' use of drugs under the policy and veterinarians are not required by FDA to submit any data on their use of the policy. According to CVM officials, decisions on when to use the policy are subjective, and it would be difficult to determine if such a subjective decision was appropriate. However, although FDA's check ratings and state inspections of dairy farms include examinations of the labels of animal drugs, they do not attempt to determine whether a veterinarian has complied with the provisions of the extra-label use policy.

Although the extra-label use policy is generally nonenforceable, CVM officials strongly believe that it is necessary because some medical conditions may occur in food-producing animals for which there are no approved drugs or the approved drugs are insufficiently effective at their approved dosages or routes of administration. According to CVM and AVMA officials, without extra-label drug uses, some animals would suffer and die.[4] CVM officials believe that because animal owners and producers would not tolerate this situation, they would resort to subversive illegal behavior in order to treat their animals if their animals could not receive treatment under the extra-label use policy. CVM officials believe that at least the extra-label use policy allows for a veterinarian—trained in the practice of responsible animal medicine—to provide some leverage into what otherwise would be a totally unenforceable and perhaps harmful public health situation.

However, there are no empirical data on the true need for unapproved drug uses for the humane treatment of suffering food-producing animals. In the absence of such data, it is difficult to determine whether dairy farming practices and economics contribute to the perceived need to use drugs in an unapproved manner to treat dairy cows. Moreover, CVM does not have any data to show that veterinarians have sufficient knowledge and information to make decisions about extra-label uses, especially those involving drugs not approved for use in any food-producing animal. Much of the existing controversy surrounding extra-label drug use might be resolved if data were available from a scientific source, such as the National Academy of Sciences, on the true need for extra-label uses and

[4]Some CVM and AVMA officials argue that this might increase the risk of diseased animals entering the human food chain, which could increase the risk of food-borne illness.

whether veterinarians have sufficient information to make informed decisions on the efficacy and safety of such uses. The Academy is in the process of establishing a standing panel of experts on animal health and veterinary medicine to advise the federal government and veterinary medical profession on the care and use of animals for food, recreation, and research. Among the topics proposed for the panel to initially consider is the use and monitoring of drugs, including extra-label use. In fiscal year 1992 the Department of Health and Human Services, FDA's parent organization, committed about $25,000 for the first year of a 3-year grant to partially fund the panel. The panel is also being funded by other federal agencies and private foundations, according to an Academy official.

Veterinarian involvement does not ensure that no illegal residues remain following extra-label use of an animal drug on a dairy cow. In several cases, USDA inspectors who test for a wider range of animal drugs in meat tissue than FDA or the states test for in milk, have found illegal drug residues in food animals, including dairy cows sent to slaughter, due to veterinarians' treatment of the cows in an extra-label manner. For example, in 1992 FDA sent a warning letter to a veterinarian for not complying with the extra-label use policy. The veterinarian had prescribed and dispensed gentamicin to treat mastitis in a dairy cow. Gentamicin is not approved for use in dairy cows. When the cow was offered for slaughter, USDA detected gentamicin at 103 parts per million in the kidney tissue of the cow. There is no tolerance or safe level for gentamicin residues in tissue. However, veterinarians argue that they cannot ensure that animal owners and producers, who typically administer drugs to their animals, follow the dosage and withdrawal periods of drugs prescribed in an extra-label manner. Another concern is that many of the drugs used by veterinarians for extra-label uses are available to nonveterinarians over the counter. As such, the veterinarian/client/patient relationship on which the extra-label drug use policy is based often may not exist. Dairy farmers may copy veterinarians' extra-label uses to treat dairy cows by using over-the-counter drugs in an unapproved manner.

The extra-label use policy is CVM's attempt to deal with widespread illegal use of drugs in food-producing animals and to balance competing interests. CVM wants to ensure the safety of the food supply but does not want to interfere with veterinarians' practice of medicine. Although we focused our work on the extra-label uses of animal drugs on dairy cows, CVM's policy, and therefore its consequences, applies to all approved animal drugs used in unapproved ways on other food-producing animals, such as cattle, swine, poultry, and fish.

Drug Manufacturers May Be Discouraged From Seeking Additional Drugs Approvals

If illegal use of animal drugs, including extra-label use under CVM's policy, occurs because not enough approved drugs are available at clinically effective dosages to treat food-producing animals, then encouraging drug manufacturers to obtain approval of new drugs and uses would seem desirable. However, veterinarians' routine practice of treating dairy cows in an extra-label manner, coupled with FDA's inability to ensure that the conditions of the policy are followed, may discourage animal drug manufacturers from seeking approval of additional uses of their drugs.

According to FDA and AHI officials, pharmaceutical manufacturers have little incentive to pursue FDA approval for all possible uses of an animal drug because the high cost of some approvals may not be justified by the anticipated limited sales volume. A January 1992 FDA task force report noted that "As a matter of economics, pharmaceutical firms are more likely to seek approval only for those drugs and uses which they perceive will offer a profitable return on their investment when considering the incurred costs of development, regulatory review, and liability associated with marketing the product." According to an AHI official, in some cases manufacturers of animal drugs that could be used to treat several animals will pursue the less expensive process of applying for approval for use of their drug only on one animal. In addition, in cases where several drug companies are producing a drug that is no longer patented, a drug company has no incentive to obtain an additional approval because the other companies would benefit from the approval at that company's expense.

Under FDA regulations, animal drugs must be labeled in such a way that the labeled directions can be adequately followed in practice, by veterinarians for prescription drug uses and by nonveterinarians for over-the-counter drug uses. Under CVM's regulatory policy, if sufficient evidence shows that the labeled directions for an animal drug are not being followed in practice—that is, for example, the drug is being used routinely in an extra-label manner—the drug is no longer considered to be safe and FDA may withdraw approval of the drug. FDA withdrew approval of chloramphenicol, in part, because substantial data showed that the drug, which is highly toxic, was being extensively used in an extra-label manner on many food-producing animals, contrary to labeled directions.

Although substantial data are needed to show that conditions of a drug approval are not being followed in practice to support withdrawal of approval, FDA gathers only limited data on extra-label uses to make these determinations. For example, FDA check-rating data record only the animal

drugs found to be improperly labeled at a dairy farm and do not record properly labeled drugs used under the extra-label use policy. In addition, FDA has not attempted to obtain data on veterinarians' use and prescriptions of drugs under the policy. According to CVM officials, they have not attempted to gather these data because of the great number of veterinarians involved nationwide and FDA's limited resources.

However, such data could help FDA ensure that the conditions of the extra-label use policy are followed, as well as determine whether to withdraw approval of a drug because its conditions of use are not being followed in practice. Several options exist for collecting these data, including FDA

- working with the National Conference on Interstate Milk Shipments (NCIMS) to expand state inspections of dairy farms to include a random survey of all extra-label uses of animal drugs;
- conducting a statistically valid sample of check-rating inspections to record data on all extra-label drugs found in dairy farm drug cabinets, not just improperly stored or labeled drugs; or
- requiring veterinarians, as a condition of the extra-label use policy, to report to FDA, in a usable form, summary information on all extra-label uses and prescriptions.

During our review, officials from AVMA and AHI stated that more information on actual extra-label drug uses is needed. However, AVMA officials expressed concern about veterinarians reporting extra-label uses to FDA because of the possibly self-incriminating nature of reporting violations of the law. FDA officials also expressed concern about the volume of paperwork that would be involved because of the extensive practice of extra-label uses. Although the basis of these concerns underscores the problem with routine extra-label uses, FDA could explore conducting a statistically valid blind survey of veterinarians for this information, perhaps in conjunction with AVMA.

Recent Proposals to Address Problems With Extra-Label Uses Have Limitations

In our 1990 report we concluded that CVM's extra-label use policy complicated FDA's efforts to ensure the safety of the nation's milk supply. We recommended that FDA reassess the appropriateness of its policy. In response, CVM has conducted meetings with representatives from consumer groups, AVMA, and AHI to discuss the pros and cons of the policy and options to further tighten its conditions. CVM also convened a task force to examine options to further enforce the extra-label use policy. In

addition, consumer groups and AVMA and AHI have made their own proposals—from phasing out the policy to amending FFDCA to specifically legalize extra-label uses. All of the proposals have been controversial because of the persistent lack of data on the need for extra-label drug use on food-producing animals, and the practical consideration of FDA's basic inability to take enforcement actions against illegal drug uses. According to the Director, CVM, extra-label drug use is the most visible public issue facing CVM.

In January 1992 CVM issued a task force report on the enforcement of the extra-label use policy. The report determined that a multifaceted enforcement plan is needed to achieve compliance with FFDCA, but that some amount of extra-label use is necessary to effectively treat sick animals. In March 1992 the Director, CVM, concurred with most of the task force's 14 recommendations. In particular, CVM intends to revise and reissue its policy guidelines to clearly prohibit extra-label use by nonveterinarians in food-producing animals. CVM also plans to consider the likelihood of drugs being used in accordance with their approved labeling as part of approving new animal drugs. In addition, in cases where FDA develops sufficient data to determine that repeated extra-label use violations involve highly toxic animal drugs, the agency may withdraw approval or conditions of use as it did with chloramphenicol. The task force report also made several recommendations to increase the level of effort for enforcement cases and training, but the Director was not optimistic that these efforts would be funded.

AHI and AVMA filed a joint citizen's petition with FDA on October 21, 1991, to provide for the approval of additional label claims for animal drugs used under the supervision of a licensed veterinarian. Under the proposal, referred to as professional labeling, FDA would allow animal drug manufacturers to obtain an increase in dosage or a dose range for a drug, eliminating the need for costly additional approvals for different dosages. In addition, the proposal would allow drug companies to use publicly available information, as well as information based on past drug approvals, to establish the safety and effectiveness of drug dosages. FDA's Veterinary Medical Advisory Committee has recommended that FDA consider this proposal. As of July 1992 FDA was still considering it. Both AHI and AVMA recognize that the proposal would address only part of the extra-label use problem. However, professional labeling may be one way of developing a fast-track process that encourages drug manufacturers to seek approval of higher dosages for their drugs.

In May 1992 legislation was introduced into the Congress to amend FFDCA to legalize extra-label uses of animal drugs.[5] The bills would permit veterinarians to use an approved animal drug, or an approved drug intended for human use, for therapeutic purposes in animals in a manner that is not specified on the label of the drug, if a valid veterinarian/client/patient relationship exists. The bills would require that the Secretary of the Department of Health and Human Services, FDA's parent organization, establish regulations governing the conditions for extra-label use. In supporting the measure, AVMA officials and others argue that the current law does not provide sufficient flexibility to recognize important advances in science and clinical animal health practices and medicine therapies that often outpace new drug and use approvals. FDA officials also believe that greater flexibility is needed because new pathogens (disease-causing microorganisms) emerge and old ones adapt that challenge the clinical effectiveness of approved drug uses. AVMA officials believe that FFDCA should be amended to allow for the discretionary use of FDA-approved drugs by licensed veterinarians similar to the discretion accorded physicians using human drugs.

However, legalizing extra-label drug uses on food animals may further undermine the animal drug approval process because drug companies would have even less incentive than they currently do to seek additional approvals of their drugs. Furthermore, legalizing extra-label uses would not eliminate the problem of illegal and/or unsafe residues in food because FDA and state officials would still lack methods to detect residues of drugs used in an extra-label manner in food.

Conclusions

Because of limited enforcement of extra-label uses, FDA does not have control over illegal use of drugs on dairy cows and residues that result in milk. In addition, the routine nature of extra-label uses and the general lack of enforcement effectively discourage animal drug companies from seeking FDA approval of additional drugs and uses.

Neither eliminating nor legalizing the extra-label use policy would solve the underlying problem of lack of FDA control over illegal animal drug use. FDA officials strongly believe that eliminating the policy would only exacerbate illegal uses by nonveterinarians, which might cause a more extensive and dangerous public health situation. Given the limitations of existing data, it is not possible to state whether the policy per se is or is not a net benefit to public health and animal welfare. At the same time, the

[5]See S. 2667 and H.R. 5297.

lack of safety and efficacy data on drugs used in an extra-label manner raises questions as to whether veterinarians have sufficient information to make informed decisions about extra-label uses. Data from a scientific source, such as the National Academy of Sciences, on the need for extra-label uses and whether veterinarians have sufficient information to make informed decisions on extra-label uses could help policy makers decide whether to keep, revise, or eliminate the controversial policy.

Further restricting extra-label uses under CVM's policy could reduce the inherent risks associated with using drugs in an extra-label manner. Furthermore, developing data on veterinarians' use and prescriptions of drugs under the extra-label use policy could give FDA the information it needs to determine whether the conditions of the policy are being followed as well as help determine whether to withdraw approval of a drug because its conditions of use are not being followed in practice.

Some extra-label uses involve using higher-than-labeled dosages of otherwise approved drugs. Yet, because of the complexities and costs of obtaining approval for higher doses, drug companies are discouraged from seeking such approvals. Professional labeling of animal drug products may be one way of developing a fast-track process that encourages drug manufacturers to seek FDA approval of higher dosages for their drugs.

Recommendations

Because insufficient data are available to fully address some of the difficult public policy and animal welfare issues related to extra-label use of approved drugs on food-producing animals, we recommend that the Commissioner, FDA, request that the new National Academy of Sciences' panel on animal health and veterinary medicine give priority to evaluating the need for extra-label uses and whether veterinarians have sufficient information to make informed decisions on the efficacy and safety of extra-label uses. The Academy could also explore alternatives for FDA to take enforcement actions when drugs are used in an illegal manner on food-producing animals.

In the interim, we recommend that the Commissioner, FDA, take the following actions:

- Revise the extra-label use policy to further restrict its use, such as to specifically preclude the use of drugs not approved for use in at least one food-producing animal species.

- Obtain data on veterinarians' extra-label use and prescriptions of drugs to determine (1) whether, and to what degree, the conditions of the policy are followed and (2) whether to withdraw approval of a drug because its labeled directions are not being followed in practice—that is, the drug is used extensively in an extra-label manner. FDA could consider several of the options discussed in this chapter for collecting the data.

  Furthermore, the Commissioner, FDA, should consider options, such as professional labeling, to develop an expedited approval process that would encourage animal drug manufacturers to seek approval of new dosage claims and proper withdrawal periods.

Eighty-Two Drugs Known to Be or Suspected of Being Used on Dairy Cows That May Leave Residues in Milk

Animal drug	Approved for dairy cows?[a]	Tolerance/safe level (ppb)[b]	Commonly used or residues of concern[c]
Acepromazine	No		X
Adenosine monophosphate	No		
Amikacin	No		X
Ammonium sulfate	No		
Amoxicillin trihydrate	Yes	10/-	X
Ampicillin	Yes	10/-	X
Apramycin	No		X
Bacitracin	No	500/-	X
Benzathine penicillin g	No		X
Betamethasone acetate	No		
Butorohanol tartrate	No		
Carbamolcholine chloride	No		
Ceftiofur sodium	Yes	[e]	X
Cephapirin	Yes	20/-	X
Chloramphenicol	No		X
Chlorobutanol	No	0/-	
Chlorothiazide	Yes	[d]	X
Chlorpheniramine	No		
Chlortetracycline	Yes	0/30	X
Cloprostenol sodium	Yes	-/.15	X
Clorsulon	No		X
Cloxacillin	Yes	10/-	X
Coumaphos	Yes	500/-	X
D-panthenol	No		
Demeclocycline	No		X
Dexamethasone	Yes	[d]	X
Dihydrostreptomycin	Yes	0/125	X
Dipyrone	No		X
Doxapram	No		
Doxycycline	No		X
Erythromycin	Yes	0/50	X
Flunixin	No		X
Furosemide	Yes	[d]	X
Gentamicin (topical)	Yes	-/30[e]	X
Glycopyrolate	No		
Griseofulvin	No		

(continued)

Animal drug	Approved for dairy cows?[a]	Tolerance/safe level (ppb)[b]	Commonly used or residues of concern[c]
Hetacillin	Yes	10/-	X
Hydrochlorothiazide	Yes	[d]	X
Isoflupredone acetate	Yes	[e]	X
Ivermectin	No		X
Kanamycin	No		X
Levamisole	No		X
Lincomycin	No	-/150	X
Methacycline	No		X
Methocarbamol	No		
Methylene blue	No		X
Minocycline	No		X
Morantel tartrate	Yes	-/400	X
Neomycin	Yes	150/-	X
Neostigmine	No		
Nitrofurazone (topical)	Yes	[e]	X
Novobiocin	Yes	100/-	X
Oxytetracycline	Yes	-/30	X
Phenylbutazone	No		X
Penicillin g	Yes	0/5	X
Penicillin potassium	No		X
Pralidoxime	No		
Prednisolone	No	0/-	X
Prednisone	No	0/-	X
Progesterone	No		
Pyrilamine maleate	No		X
Salicylic acid	Yes	0/-	
Sodium salicylate	No		
Spectinomycin	No		X
Sulfachloropyridazine	No	-/10	X
Sulfadiazine	No	-/10	X
Sulfadimethoxine	Yes	10/-	X
Sulfamerazine	No	-/10	X
Sulfamethazine	No	-/10	X
Sulfamethizole	No	-/10	X
Sulfamethoxazole	No		X
Sulfanilamide	No	-/10	
Sulfapyridine	No	-/10	X

(continued)

Animal drug	Approved for dairy cows?[a]	Tolerance/safe level (ppb)[b]	Commonly used or residues of concern[c]
Sulfaquinoxaline	No	-/10	X
Sulfathiazole	No	-/10	X
Tetracycline (topical)	Yes	-/80[e]	X
Thiabendazole	Yes	50/-	X
Trichlormethiazide	Yes	[d]	X
Trimethoprim	No		X
Tripelennamine hydrochloride	Yes	[d]	X
Tylosin	Yes	50/-	X
Xylazine	No		X
Subtotal			
Approved	30	30[f]	29
Unapproved	52	14	35
Total	**82**	**44**	**64**

[a]FDA has approved at least one use of the drug in or on dairy cows. However, use of an approved drug in an unapproved manner could result in separate residue concerns.

[b]Value indicates tolerance and/or safe level for drug residues in milk set by FDA in parts per billion (ppb).

[c]According to FDA's Center for Veterinary Medicine (CVM) compliance and surveillance data and information from CVM's test development activities, these drugs are commonly used on dairy cows or CVM plans to develop methods to test for residues of these drugs in milk because potential residues could pose a health concern to consumers.

[d]FDA did not establish a tolerance for residues of this drug in milk but did establish a milk discard time. If the drug is used according to the FDA-approved label and the milk discard time is followed, FDA determined that no residues of concern would result in milk. However, if the drug is used in an unapproved manner, and/or the milk discard time is not followed, residues may result in milk.

[e]FDA has approved these five drugs for at least one use on dairy cows, and the drugs are not expected to leave residues in milk when used in an approved manner (e.g., topical). However, FDA data indicate that the drugs may leave residues in milk when used in an unapproved manner (e.g., injected). FDA has set safe levels for residues in milk for some of the drugs when they are used in an unapproved manner.

[f]This subtotal includes drugs approved for at least one use on dairy cows and for which FDA has established a tolerance, safe level, or milk discard time, and those drugs from note e.

Source: Prepared by GAO using data from multiple sources, including FDA and USDA (see ch. 2).

Definition of a Veterinarian/Client/Patient Relationship

The American Veterinary Medical Association defines a valid veterinarian-client-patient relationship as follows:[1]

An appropriate veterinarian-client-patient will exist when: (1) the veterinarian has assumed the responsibility for making medical judgments regarding the health of the animal(s) and the need for medical treatment, and the client (owner or other caretaker) has agreed to follow the instructions of the veterinarian; and when (2) there is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept; and when (3) the practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.

[1]See FDA Compliance Policy Guide 7125.06, "Extra-Label Use of New Animal Drugs in Food-Producing Animals."

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