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

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FOOD SAFETY AND QUALITY

FDA Surveys Not Adequate to Demonstrate Safety of Milk Supply

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November 1, 1990

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

Dear Mr. Chairman:

In your April 2, 1990, letter, and in subsequent discussions with your office, you asked us to review the adequacy of the surveys the Food and Drug Administration (FDA) conducted in 1988 and 1990 to determine the presence of selected antibiotic drug residues in milk and whether the information developed provided a sufficient basis for FDA's public statements on the safety of the milk supply.

FDA is responsible for assuring the safety of the billions of gallons of milk produced in the United States each year, as well as numerous other food, drug, and cosmetic products. FDA oversees the nation's milk supply through a cooperative program with all states and the District of Columbia (states). Generally, the states carry out the day-to-day oversight of the milk supply. FDA monitors the overall cooperative program, provides technical assistance, approves animal drugs for use in dairy cows, and performs studies, takes samples, and does additional testing when agency officials believe it is needed.

Concerned about media reports that independent surveys had found a variety of animal drugs (primarily antibiotics) contaminating the milk supply, FDA conducted three efforts to determine the presence of selected antibiotic drug residues in milk between 1988 and 1990. These efforts were necessary because, except for penicillins, there is no routine testing required to screen milk for such drugs, many of which are not approved for use in milk-producing dairy cows (dairy cows). FDA stated that the results of these three surveys confirmed its belief that the nation's milk supply was safe.

Results in Brief

FDA statements that the nation's milk supply was not contaminated with unsafe animal drug residues cannot be supported because limitations in the survey methodologies precluded any overall conclusions. Specifically, the surveys were not statistically valid and present, at best, "snapshots in time" of a small number of milk samples tested for the

presence of a small number of drug residues. However, collectively, because the surveys show instances of drug residues in milk, they suggest a need for more thorough examination by FDA to identify the types and amounts of animal drug residues that may be contaminating milk.

Even if the surveys had been statistically valid, the results would still be of limited use because FDA does not have test methods to detect and confirm many drugs believed to be used in dairy cows. Generally, companies submitting drugs to FDA for approval for use in food-producing animals must develop tests to identify any residues left by the drug in edible tissues or milk. However, many of the drugs believed to be used by the dairy industry were not submitted to FDA for use in dairy cows, and the tests to detect their residues in milk have not been developed. In other cases, the test methods FDA has are not sensitive enough to confirm the presence of drug residues at the health concern levels set for human consumption.

Our review, which was limited to FDA's milk surveys conducted between 1988 and 1990, raised other questions about the adequacy of routine monitoring of the milk supply by FDA and cooperating state agencies, FDA's "extra-label use" policy that permits the use of drugs not specifically approved for dairy cows, and the setting of health concern levels for unapproved drugs.

Background

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, FDA, part of the U.S. Department of Health and Human Services (HHS), is responsible for ensuring the safety of the nation's milk supply. The FDA's milk safety program is a collaborative federal/state effort that dates back to the mid-1920s. Most milk is produced and marketed under the Grade A Pasteurized Milk Ordinance (the Milk Ordinance). The Milk Ordinance is recognized by public health agencies, the milk industry, and many others as a national standard for milk sanitation.

The only official test for detecting animal drugs in milk, under the Milk Ordinance, is the Bacillus Stearothermophilus Disk Assay test (disk assay). While the disk assay effectively detects the residues of several drugs in the penicillin family, it is much less effective in detecting many of the other drugs now being used by the dairy industry. For instance, the disk assay detects sulfa drugs at levels of 15 parts-per-million (ppm) or higher—1,500 times the 10 parts-per-billion (ppb) concern level set by FDA for milk. Some states and industry groups supplement the disk assay with other tests that are more sensitive to sulfa and other drugs. FDA

itself does not routinely test milk samples for drug residues but relies instead on the states and industry for such testing. However, according to FDA Milk Safety Branch officials, FDA does not routinely receive state or industry test results.

FDA is also responsible for determining whether new animal drugs, such as antibiotics, are safe and effective for those animals and whether the food products (including milk) from treated animals will be safe for human consumption. Generally, new animal drugs may be legally marketed in the United States only if FDA has determined that they are safe and effective and has established tolerances for their intended uses.

A tolerance defines the amount of residues of a new animal drug from treated animals that is demonstrated to be safe in the human diet.[1] FDA also sets withdrawal periods for approved drugs during which time meat or milk products from the treated animal cannot be marketed. The intent is to allow the drug to be purged from the animal's system so that any residues are below the tolerance level (see app. I for more information on how FDA establishes tolerances for drug residues in milk).

Residues of drugs, including antibiotics, can occur in milk as the result of legal or illegal use of drugs. FDA has approved 53 drugs for use in or on dairy cows, including 20 antibiotic drugs. In addition, FDA has established tolerances in milk for 21 of these 53 approved drugs. Generally, an illegal use occurs when a drug residue is found that exceeds its tolerance level, when misuse of a drug approved for use in dairy cows results in residues in milk for which no tolerance has been established, or when residues of a drug not approved for use in dairy cows results in residues in milk.

Actual or intended use of a new animal drug in a food-producing animal in a manner inconsistent with the approved labeling can result in FDA taking regulatory action against the veterinarian, producer, or other persons involved. However, FDA has established guidelines for veterinarians to treat food-producing animals with drugs in an unapproved manner, if suffering and/or death would result from not treating the affected animal.

[1]Since most of the drugs FDA tested for in its surveys are not approved for use in dairy cows and have no official tolerance levels, FDA set unofficial "concern levels" for use in the surveys. Generally, these concern levels were estimated on the basis of tolerance levels established for the drugs in other animal species and tissues.

In establishing what is known as the extra-label use policy, FDA stated that it would ordinarily refrain from taking regulatory action against licensed veterinarians for using or prescribing any drugs they could legally obtain provided certain criteria are met. FDA's policy does not permit non-veterinarians (e.g., dairymen) to treat food-producing animals with drugs in an unapproved manner. In addition, FDA has declared that certain drugs cannot be used under the extra-label use policy because of public health concerns.

FDA Milk Survey Methodologies and Results

Between 1988 and 1990, FDA conducted three efforts to determine the presence of selected antibiotic drug residues in milk in response to reports from the media and others that drugs were contaminating the milk supply. In March 1988, FDA tested a total of 49 retail milk samples from 10 cities in the United States to determine the presence of sulfamethazine (SMZ), an antibiotic sulfa drug, in milk. SMZ is not approved for use in dairy cows, and its residues in milk may pose a risk for individuals allergic to sulfa-based drugs. SMZ is also a suspected carcinogen (cancer-causing agent). FDA found that 73 percent of the samples tested (36 of 49) contained SMZ levels ranging from 0.8 ppb to 40.3 ppb. Five of the 36 samples contained SMZ residues above 10 ppb, FDA's unofficial concern level for SMZ at that time.

Prompted by the 1988 survey results, FDA took several steps intended to eliminate SMZ residues in milk, including an educational campaign aimed at dairy farmers. FDA coordinated this educational effort with the National Conference on Interstate Milk Shipments (the National Conference).[2] In October 1988, the National Conference sent a questionnaire to all state milk regulatory laboratories asking for data on raw milk samples tested for SMZ from May to September 1988 to assess the effectiveness of FDA's educational program.

FDA's analysis of this follow-up survey indicated that 5 percent of reported samples tested (247 out of 4,887) contained SMZ residues and 1 percent (54 out of 4,887) contained SMZ residues above 10 ppb. Based on these results, FDA concluded that SMZ use in dairy cows had decreased significantly since its 1988 survey and the SMZ problem had been resolved.

[2]The National Conference is a voluntary organization of federal and state health and agricultural officials and the dairy industry that, along with FDA, oversees a cooperative, federal-state program (the Interstate Milk Shippers Program) to ensure the sanitary quality of milk and milk products shipped interstate.

FDA's conclusion was subsequently questioned in December 1989, when the Wall Street Journal (the Journal) reported the results of two surveys of animal drug residues in milk, one sponsored by the Journal and the other sponsored by the Center for Science in the Public Interest (CSPI), a consumer food safety and nutrition organization. The Journal survey found that 38 percent of 50 retail milk samples contained antibiotic residues, possibly including SMZ and other unapproved drugs. The CSPI survey foundthat 20 percent of 20 retail milk samples collected in the Washington, D.C., area contained sulfa drugs, again possibly including SMZ and other unapproved drugs. Both surveys used an analytical method called "Charm II." This method is considered a screening test because it reportedly detects the presence of seven classes of antibiotic drug residues, but generally cannot identify individual drugs within these classes.

In response to media reports of contaminated milk, FDA conducted another survey in 1990 to test the reliability of the independent surveys and to determine for itself the presence of animal drug residues in milk. FDA collected 70 retail milk product samples[3]—5 each from 14 cities sampled in its 1988 survey and/or the Journal survey. FDA also used the Charm II, as well as other methods, to test the milk samples.

FDA, as a matter of policy, requires further, more specific tests of all positive screening test results such as those obtained from Charm II to conclusively identify and confirm the presence of the specific drug residues present. These more specific tests include high pressure liquid chromatography (HPLC), thin layer chromatography, gas chromatography, and mass spectrometry test methods. FDA 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.

FDA's results using the Charm II test were similar to the results from the Journal and CSPI surveys in that the presence of antibiotic drug residues was indicated in many of the samples tested. In addition, the results of HPLC testing at FDA's Beltsville laboratory indicated that almost 86 percent of the samples tested (60 of 70) contained sulfa drug residues and that 11 of the samples (16 percent) had residues above the concern levels for the drugs analyzed. However, upon subsequent confirmation testing with mass spectrometry methods, FDA did not find any of the

[3]FDA collected 2 identical containers from each of 5 stores in 14 different cities and sent one of each to its Beltsville and Philadelphia laboratories, respectively.

antibiotics it tested for above established health concern levels, or above the level of detection sensitivity of the methods used.

FDA initially reported, in a February 5, 1990, press release, that it could not confirm the presence of any antibiotics in the milk samples tested in the 1990 survey. However, FDA's press release was premature because the agency had not completed its analysis of the milk samples at the time it was issued. Upon subsequent testing, FDA confirmed the presence of SMZ at levels less than 5 ppb in three milk samples tested. FDA later modified its presentation of the 1990 survey results to report this finding.

FDA's Survey Results Not Representative of the Nation's Milk Supply

FDA's efforts and the independent surveys were based on a limited number of milk samples that were not selected in a manner that would allow drawing statistically valid conclusions about the overall milk supply. At best, FDA's efforts and the independent surveys were snapshots in time of a small number of milk samples tested for the presence of a small number of drug residues.

With specific regard to FDA's initial 1988 survey and its 1990 effort, a total of 119 milk samples were tested—a very small percentage of the overall milk supply. In addition, the milk products and samples were not randomly selected for these surveys.

FDA's 1988 follow-up to its initial 1988 survey is not comparable and does not show that the SMZ problem initially found in its survey of 10 cities was corrected. First, the 23 states that responded to the survey that tested milk samples produce only about 65 percent of the nation's milk supply annually. More importantly, FDA could not provide documentation to show how the responding states had sampled milk products. If the testing states did not use statistical methods to obtain sample data, then the resulting state and national data are highly suspect. FDA also did not know whether the analytical methods and calibration standards used by the testing states to detect SMZ residues were similar or whether the methods used were all capable of detecting SMZ residues at the 10 ppb health concern level used by FDA at that time.

We cannot state definitely that the SMZ results FDA developed from its 1988 follow-up effort are flawed. However, with a sample representing only 65 percent of the milk supply, no assurances that state samples were statistically drawn, and questions regarding the comparability of

the testing performed, for the FDA estimates to be correct would likely be coincidence.

Limited Number of Drugs Tested

In FDA's 1988 and 1990 survey efforts, only a limited number of drugs were tested in comparison to the total number of animal drugs that might have been present in milk products. Approximately 78 drugs, approved and unapproved, are believed to be used in the dairy industry. During its surveys, FDA did not test milk samples to determine generally whether many of the 53 drugs approved for use in or on dairy cows were present, or for many of the approximately 25 drugs not approved for use in dairy cows but believed to be used in the dairy industry.

In its 1988 survey and subsequent follow-up effort, FDA only tested for or collected information on one drug—SMZ. Also, while FDA used the Charm II test to screen the 1990 survey samples for the presence of seven classes of antibiotics, FDA only had methods available to confirm the presence of six of the antibiotics included in its survey.

FDA has also observed that drugs used to treat dairy cows are to some extent chosen because testing is not being performed to detect them, or the drugs cannot be detected by available test methods. Consequently, testing for a limited number of drug residues in sampled milk products does not provide information on the presence of other drugs that might be in milk and may not provide sufficient information to support broad conclusions on the safety of the milk supply.

Some Drugs Not Detected at Their Concern Level

FDA does not know what additional test methods states use to sample milk or whether such tests can detect some drugs at their concern level. For instance, regarding the 1988 follow-up survey, FDA did not have information on whether the 23 states that reported test results data used test methods sensitive enough to detect SMZ residues at the then 10 ppb concern level. Some states may have used only the disk assay which is the only official screening test for detecting antibiotic drug residues in milk under the Milk Ordinance. While the disk assay is effective for detecting penicillins, it cannot detect many other antibiotics (including SMZ) at the concern levels established by FDA. Although FDA officials believe that some states had other test methods available to detect SMZ residues, they do not know what methods the states used. If the reported results were based on the official disk assay method alone, then the results might have understated the number of samples containing SMZ above the FDA concern level.

In addition, some of the analytical methods used in FDA's 1990 survey efforts were unable to detect and/or confirm some drug residues at concern levels. For example, FDA discounted Charm II screening test results which indicated the presence of novobiocin residues in five of the samples tested on the basis of another screening test method that was not as sensitive as the detection capability claimed for the Charm II. Furthermore, this second screening method could not detect novobiocin at the health concern level established by FDA.

FDA also requires that survey screening test results indicating the presence of illegal or unapproved drug residues be confirmed using mass spectrometry testing, to facilitate its ability to take regulatory action. However, in its 1990 survey, FDA only had mass spectrometry methods for six drugs, and three of these methods were incapable of confirming the presence of their drugs at the health concern levels established. Specifically, three of the six drugs for which FDA had confirmatory tests were chlortetracycline, oxytetracycline, and tetracycline. FDA-established concern levels for these three antibiotics were/are 30, 30, and 80 ppb, respectively. However, FDA's mass spectrometry methods could only confirm the presence of these drugs at levels of 100 ppb or more. Thus, although FDA reported that it could not confirm the presence of any tetracycline drugs, the drugs may still have been present in amounts exceeding the concern level, but below the level of the confirming test's sensitivity.

Additional questions have been raised about FDA's handling of the milk samples and use of analytical procedures in its 1990 survey. These and other limitations are discussed further in appendix II.

Other Concerns Relating to Drug Residues in Milk

During this review, several related issues were identified that we believe merit further study. However, they were beyond the scope and time available for completing this work. Specific issues include the (1) adequacy of routine drug residue screening in milk by FDA and the states, (2) impact of FDA's extra-label use policy as it relates to dairy cows, and (3) setting of unofficial concern levels for unapproved drugs based on limited data.

Routine Drug Residue Testing May Be Inadequate

Neither FDA nor the states routinely screen milk for many of the drugs, approved or unapproved, that might be used by the dairy industry. With regard to antibiotic drugs, the only screening test officially sanctioned by the Milk Ordinance is effective primarily for detecting the

penicillin family of drugs, not the sulfa, tetracycline, or other drug families. FDA is also aware that the choice of unapproved drug used is often guided by the fact that regulators cannot detect or are not checking for that drug. For these reasons FDA had to undertake the surveys discussed in this report.

Some states, veterinarians, and industry organizations, concerned that the Milk Ordinance's official screening test for antibiotic drug residues is not effective in detecting drugs other than penicillins, have asked FDA to either develop reliable and inexpensive methods for their use or officially sanction some of the commercial tests that some states already use such as the Charm II method. However, according to the Deputy Director, Center for Veterinary Medicine, FDA does not have the legislative authority to approve or sanction screening tests that are not submitted as part of a sponsor's application for a new animal drug approval.

According to FDA attorneys, screening test kits by themselves are considered animal devices under FFDCA and, as such, are not subject to premarket review and approval by FDA. However, such kits are subject to post-marketing controls under the law. Thus, for example, the labeling of screening test kits must be truthful, accurate, non-misleading, and must bear adequate directions for use. FDA does have the authority to evaluate commercially available screening test kits and publish the results of such evaluations.

FDA plans to exercise its evaluation authority in order to assist the states and the dairy industry in determining/obtaining effective and reliable analytical methods for detecting animal drug residues in milk. Starting with sulfa drugs, FDA intends to collect information on commercially available screening tests, conduct limited evaluations of such tests—including their capabilities to detect residues at or above the tolerance or other levels established by FDA, and make the results of these evaluations publicly available.

Extra-Label Drug Use Makes Oversight Difficult

FDA's efforts to oversee the safety of the nation's milk supply are complicated by the use of drugs not specifically approved for use in dairy cows and the extra-label use policy that allows it. In brief, this policy allows veterinarians to use drugs in an unapproved manner on animals if that animal's life is in danger, and no other effective approved drugs are available.

No illegal drug residues are supposed to result from the extra-label use of drugs in dairy cows. However, neither FDA nor drug companies have performed the studies necessary to establish the dosage levels and withdrawal periods needed to ensure that illegal/unsafe residue levels do not result in milk from extra-label uses. The lack of such scientific data makes it difficult for veterinarians to determine and prescribe dosages and withdrawal times that will assure illegal residues do not occur. Another concern is that some of these drugs are available to the layman "over-the-counter." As such, the veterinarian/client relationship on which the extra-label drug use policy is based often may not exist.

FDA also has not determined what "safe" milk residue levels are for many of the drugs used in extra-label dairy applications. Instead, FDA has set unofficial concern levels for a limited number of these drugs, primarily for the 1990 survey. FDA's general practice is to not take regulatory action when residues are found at levels below the concern level.

Many of the residues detected in FDA's 1988 and 1990 milk surveys were from drugs not approved for use in dairy cows. Because of FDA's policy that allows the extra-label use of drugs by veterinarians and its general practice not to take action when drug residues are below the concern level, it is difficult to determine whether residues found in milk result from the improper use of drugs by veterinarians under the extra-label use policy or from illegal use by non-veterinarians.

The Adequacy of Concern Levels Is Questionable

Many of the drugs tested for in FDA's 1990 survey are not approved for use in dairy cows and there are no official tolerance levels established for their presence in milk. As a result, FDA conducted a health risk assessment to determine unofficial drug residue concern levels for selected drugs targeted in its survey efforts. FDA estimated the concern levels for residues in milk on the basis of tolerances established for the drugs in other animal species or tissues or on other data. Questions exist about (1) the reliability of setting levels in this manner, (2) how factors such as the aggregate and synergistic health effects of the drugs were handled, and (3) whether drug metabolites,[4] both individually and those of closely related drugs, should be included in assessing health effects.

[4]Drug compounds administered to food-producing animals can form or be broken down into new substances (metabolites and degradation products of the compound) by the animal's biological systems, which 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 because of the use of the parent compound.

FDA regards allergic responses to penicillin, tetracycline, and/or sulfa drugs as a serious public health concern. Studies conducted by FDA's National Center for Toxicological Research also indicate that moderate-to-high doses of the sulfa drug SMZ cause thyroid cancer in some laboratory animals. In addition, FDA data suggest that if a structural feature in one compound is found to cause cancer, the presence of that same structural feature in other compounds greatly increases the probability that they too can cause cancer. All of the sulfa drugs have very similar structures. According to FDA data, some of these drugs exhibit toxic effects similar to those produced by SMZ.

In setting concern levels for the 1990 milk survey, however, FDA allowed residues of up to 10 ppb for each sulfa drug and did not consider the aggregate or synergistic effect of these drugs. The results of FDA's HPLC screening tests for the 1990 survey indicated that 46 percent (32 out of 70) of the samples tested contained more than one sulfa drug residue.

FDA data also indicate that drug metabolite residues in food are an important consideration. FDA states that the importance of any metabolite in terms of its level, persistence, structure, relationship to the parent drug, and the anticipated human exposure must be considered in deciding about the need for separate toxicity testing. According to FDA, drug metabolites are likely to present health risks which 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, the SMZ metabolite levels that develop in pork are 3 to 10 times higher than the detectable residue level of the parent drug.

FDA suspects that metabolites may also be present in milk when drug residues are found and is currently attempting to determine the amount of SMZ metabolites that may be "hidden" in milk. According to FDA data, several of the metabolites that develop from this drug in milk may present carcinogenic risks similar to those associated with SMZ itself. However, metabolites could not be detected by the analytical methods FDA used in the milk surveys, and, as a result, the metabolite levels that might be found in milk were not considered.

Conclusions

FDA's efforts to determine the presence of animal drug residues in milk, as well as the independent surveys, were not statistically designed to be representative of the nation's milk supply. Thus, the surveys do not provide an adequate basis for the statements made by FDA regarding the nation's milk supply. However, collectively, because the surveys show

instances of drug residues in milk, they suggest the need for more thorough examination to identify the types and amounts of animal drug residues that may be present in milk.

Furthermore, if FDA had designed and undertaken a statistically valid random sample of milk products to test for drug residues that was representative of the nation's milk supply—a difficult and costly endeavor—the results would still be of limited value because FDA lacks test methods to detect and confirm most of the drugs believed to be used in dairy cows, and some of FDA's test methods cannot detect drug residues at the concern level set for human consumption.

The only screening method sanctioned by the Milk Ordinance for antibiotic drug residues in milk, by itself, will not effectively detect most drugs currently used by the dairy industry. Some states are supplementing the Milk Ordinance's sanctioned screening test with other commercially available methods that are reportedly capable of detecting more drug types.

Although FDA may lack sufficient legislative authority to officially sanction screening test methods that are not part of an application for new drug approval, FDA can exercise its authority to evaluate commercially available screening test kits and share the results of its evaluations with the states, industry, and others. Beginning with sulfa drugs, FDA plans to assist the states and others by conducting these evaluations and publicizing the results.

FDA has also begun to develop new test methods capable of detecting and confirming specific drugs at established concern levels. However, there are many additional drugs, approved and unapproved, for which adequate tests do not exist. These and other limitations in testing capability detract from FDA's ability to ensure the safety of the milk supply.

Finally, FDA's regulatory efforts to ensure a safe milk supply are made more difficult by the extra-label use of drugs in an unapproved manner in dairy cows and by questions regarding the basis for setting unofficial concern levels and how to treat factors like the cumulative effect of closely related drugs and drug metabolites.

Recommendations

Because of insufficient data to fully address many of the issues discussed in this report, and recognizing that it is unlikely that FDA could

devote a large amount of its limited resources to this one issue, we recommend that the Secretary, HHS, direct the Commissioner, FDA, to take several incremental actions to provide greater assurance that the milk supply is safe.

First, FDA should develop more complete information on the incidence of drug residues in milk. FDA should begin by asking the states under their cooperative agreements and the dairy industry to routinely provide them with the results of their screening tests for drug residues in milk, as well as information regarding their sampling plan and the types and sensitivities of test methods employed.

Second, to further assist state regulatory efforts, FDA should work with the states to evaluate commercially available screening tests and encourage that those found effective for sulfa, tetracycline, and other drugs, be included in the Milk Ordinance as a supplement to the disk assay, which is primarily effective only for penicillins. If FDA determines that it needs additional legislative authority to approve screening tests apart from new drug applications, then it should seek such authority from the Congress.

Third, FDA should prioritize and expedite its current efforts to develop and evaluate new screening and confirmatory test methods for animal drug residues in milk, possibly according to the health risks they perceive to be associated with the individual drugs involved.

Fourth, FDA should work closely with the states to confirm, possibly on a random basis, the types and amounts of drug residues found in state screening samples. If this information and confirmatory testing indicates that potential problems exist, FDA should work with the states to further expand testing.

Last, if the additional information developed from increased screening and confirmatory testing indicates that widespread problems exist from the misuse of drugs approved and/or unapproved for use in dairy cows, FDA should reassess the appropriateness of its policies on extra-label drug use and its use of concern levels as a trigger for regulatory action.

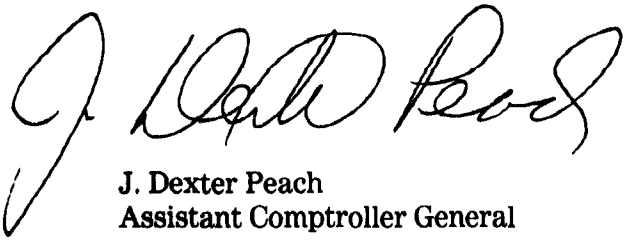
Our work was conducted from April to September 1990 at FDA headquarters and field locations in the Washington, D.C., metropolitan area. (Further details on our objectives, scope, and methodology are provided in app. III.)

We discussed the information in this report with officials in FDA's Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, and Office of Regulatory Affairs. Where appropriate, some changes have been made based on the discussion to further clarify the information presented. However, as requested by your office, we did not obtain official agency comments on a draft of this report.

As arranged with your office, unless you publicly announce its contents earlier, we will make no further distribution of this report until 30 days after the date of this letter. At that time we will send copies to the Secretary, HHS; the Commissioner, FDA; interested congressional committees; and other interested parties 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 are listed in appendix IV.

Sincerely yours,



J. Dexter Peach
Assistant Comptroller General

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Abbreviations

ADI	acceptable daily intake
CDC	Centers for Disease Control
CFSAN	Center for Food Safety and Applied Nutrition, FDA
CSPI	Center for Science in the Public Interest
CVM	Center for Veterinary Medicine, FDA
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
GAP	Government Accountability Project
HHS	U.S. Department of Health and Human Services
HPLC	high pressure liquid chromatography
ppb	parts-per-billion
ppm	parts-per-million
SMZ	sulfamethazine

Federal Regulation of Drug Residues in the Milk Supply

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended (21 U.S.C. 301 et seq.), the Food and Drug Administration (FDA) is responsible for ensuring the safety and purity of the nation's milk supply. In addition, FDA is required to determine whether new animal drugs for use in food-producing animals,[1] such as antibiotics for use in milk-producing dairy cows (dairy cows), are safe and effective for those animals and whether the edible products derived from treated animals, such as milk, will be safe for human consumption. Under FFDCA and FDA policy, food items containing unapproved animal drug residues that may be harmful to humans are considered to be adulterated and subject to regulatory action.

Tolerance Setting Process

Generally, a new animal drug may be legally marketed in the United States only if FDA has determined that it is safe and effective and has established tolerances for its intended uses. A tolerance is a legally binding limit that defines the amount of residues of a new animal drug in edible tissue (or other edible products such as milk) from treated animals that is demonstrated to be safe in the human diet.

FDA uses toxicology and residue data to assess possible health risks of an animal drug residue in milk and determine the tolerance level that will protect the public health within a practical certainty. The risk of a drug residue depends on both the toxicity of animal drug residues (i.e., their potential to cause adverse health effects in humans) and potential human exposure to residues in the diet.

Sponsors of new animal drugs must submit data to FDA that substantiates the safety and effectiveness of the proposed drug. The data must be specific for each use and species of animal for which the drug is intended and, for food-producing animals, must include evidence showing the safety of residues of the drug (including metabolites[2]) and acceptable methods for recovering and measuring such residues from edible products.

[1]Under FFDCA, new drugs are drugs that are not generally recognized by qualified experts as safe and effective for their labeled uses.

[2]Drug compounds administered to food-producing animals can form or break down into new substances (metabolites and degradation products of the compound) by the animal's biological systems, which 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 because of the use of the parent compound.

FDA's risk assessment process for animal drug residues in milk has six steps:

1. Identifying the nature and amount of residues from the parent drug and its metabolites and the depletion of the residues after treatment.

2. Comparing the metabolism of the drug in the animal species proposed for the toxicity testing with the metabolism of the drug in the animal targeted for treatment (to determine which residues must be tested for toxicity and which laboratory animal species to use for toxicity studies).

3. Determining the toxic effects of residues, if any, from sponsor-submitted studies and the safe concentration of all residues from the proposed drug.

4. Identifying which residue to measure as an indicator of the safe concentration of all residues and establishing a tolerance for that residue (referred to as the "marker residue").

5. Evaluating the analytical method proposed by the sponsor to measure the marker residue reliably in milk at the tolerance level (referred to as the "regulatory method").

6. Establishing the withdrawal period for the administered drug to ensure the depletion of residues at or below the safe concentration level as indicated by the marker residue (when the marker residue is at or below its tolerance level) so the milk can be safely consumed. (FDA does not establish a tolerance when residues above the safe concentration are unlikely to occur at zero withdrawal.)

For non-carcinogenic drugs, FDA establishes the safe concentration for the drug residues based on the acceptable daily intake (ADI) for the drug. Adjustments are made for differences between test animals and humans in food consumption versus body weight, a safety factor, and the estimated amount of milk consumed by an individual per day. The ADI is the estimated daily intake of a drug residue which, during a lifetime of exposure (70 years), is not expected to cause appreciable health risks on the basis of all known facts at the time. The ADI is based on the highest drug dosage demonstrated to have no observable effect in the most sensitive test animal species used in the toxicity studies divided by a safety factor.

The safety factor is intended to provide a margin of safety and account for the inherent uncertainty in projecting the results of animal toxicology tests to humans. FDA uses safety factors of 100 to 1,000 depending on the nature of the effects observed at the higher dosage levels in the test animals and the length of the study.

FDA then calculates the safe concentration using the ADI, the weight of the average adult (60 Kg), and the maximum amount of milk that FDA estimates an individual can consume per day—1.5 liters. FDA's calculations assume that all dairy cows are treated with the drug and thus an individual will consume 1.5 liters of milk containing the drug residues per day, assumptions which FDA officials believe overstate a person's likely exposure to actual drug residues in the milk supply.

For drug residues that are carcinogens, FDA determines the dose that will satisfy the "no residue" requirement of FFDCA to establish the safe concentration level. Under FFDCA, FDA cannot approve a new animal drug if the drug induces cancer in humans or animals unless (1) the drug will not adversely affect the animals for which it is intended and (2) no residue of the drug is found by methods approved by FDA regulation, in any edible portion of the animals after slaughter or in any food derived from the living animals. FDA has operationally defined "no residue" to mean no significant risk of cancer—corresponding to a risk to test animals of no more than 1 in 1 million over a lifetime of drug exposure. FDA calculates the concentration of drug residue yielding no significant risk of cancer level from the tumor data using a statistical extrapolation procedure.

Unlike the risk assessment process used for other health effects of drugs, FDA does not use an acceptable daily intake in assessing carcinogenic effects. The ADI is a level of drug intake which is safe within a practical certainty. Scientists have been unable to determine whether a safe, threshold level exists for carcinogens because the mechanisms that produce cancer are not completely understood. Therefore, lacking information establishing the mechanism of carcinogenesis for a particular drug residue, FDA uses dose-response models which assume that some risk of contracting cancer exists for even minute exposures to carcinogenic drug residues. Dose-response assessment defines the relationship between estimated dietary exposure to a carcinogen and the probability of carcinogenic effects.

There is no tolerance established for sulfamethazine (SMZ) in milk because FDA has not approved its use in milk-producing dairy cows. If a

veterinarian or farmer uses SMZ in dairy cows, illegal drug residues in milk can result. Recently, FDA estimated that treatment of just a single cow with SMZ can contaminate the milk, when pooled, of 70,000 cows.

Concern Levels

When tolerances do not exist or cannot be calculated because the necessary toxicology and residue data are not available, FDA may set "concern levels" for drug residues. For milk, these levels correspond to the lowest level of the drug residue that can be quantified by an analytical method or one-third of the lowest published tolerance for the drug residue in edible tissue.

Concern levels are not official tolerances and do not represent FDA approval of the drug use. Rather, these values represent an informal level of action/concern that FDA uses 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 the drug.

In the past, FDA has approved certain animal drugs and established a zero tolerance for their residues, based on the specified analytical method available at that time. The sensitivity level of the available method then, in essence, became the "action level" for these residues. For example, FDA initially set a zero tolerance for erythromycin, an antibiotic used to treat infections in dairy cows. However, the lowest level quantifiable in milk using the analytical method accepted when the zero tolerance was established was 50 parts-per-billion. Consequently, for regulatory purposes, FDA has "operationally" defined this tolerance at 50 ppb.

FDA's Center for Veterinary Medicine (CVM) has determined that safe levels cannot be established for the drugs chloramphenicol and SMZ, because of human food safety concerns. FDA policy states that neither of these drugs should be used in dairy cows because there is concern about any detectable level of the drugs in milk. However, SMZ, which is available over-the-counter, is approved for cattle, dairy cows that are not producing milk, swine, chickens, and turkeys in order to treat respiratory diseases and, in some instances, to promote weight gain.

Sulfamethazine Level of Concern

SMZ residues in milk and other food products have become a concern to FDA because the drug has been shown to be carcinogenic in laboratory animals. Two animal studies conducted by FDA's National Center for Toxicological Research have demonstrated that moderate-to-high doses

of SMZ produced thyroid tumors in laboratory rats and mice. FDA is considering whether to permit continued use of SMZ as currently approved.

Controversy exists within FDA as to whether a safe level can be set for SMZ because the data necessary to make such a determination are incomplete. However, CVM has calculated a concern level for total residues of SMZ in milk to be 12 ppb (for the parent compound and its metabolites combined), on the basis of a preliminary risk assessment using available toxicology data. CVM estimates that total SMZ residues of 12 ppb over a lifetime of exposure may present no more than an insignificant risk of cancer in humans. However, existing safety data do not allow a marker residue to be established. CVM estimates that if the parent drug SMZ was used as the marker residue, then the concern level would be in the 1 to 5 ppb range. CVM believes that the low levels of SMZ projected to be safe in milk will preclude practical use of the drug in dairy cows.

Approved and Unapproved Drug Use in Dairy Cows

Residues of drugs, including antibiotics, can occur in milk as the result of legal or illegal use of drugs. FDA has approved 53 drugs for use in or on dairy cows, including 20 antibiotic drugs. FDA has established tolerances in milk for 21 of the 53 drugs approved for use in dairy cows.[3] In addition, about 25 drugs, including 12 antibiotics, not approved for use in dairy cows are believed to be used in the dairy industry. Generally, an illegal use occurs when a drug residue is found that exceeds its tolerance level, when misuse of a drug approved for use in dairy cows results in residues in milk for which no tolerance has been established, or when residues of a drug not approved for use in dairy cows results in residues in milk.

Under FFDCA, the actual or intended use of a new animal drug in a food-producing animal in a manner inconsistent with the approved labeling causes the drug to be adulterated. FDA may consider taking regulatory action against the veterinarian, producer, or other persons involved, whenever such actual or intended unapproved use is found.

[3]FDA has not established tolerances for many drugs approved for use in or on 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 residues of the drug above its safe concentration level would be unlikely to occur at zero withdrawal. Also, tolerances in milk exist for four drugs, for which the approval of their uses in dairy cows has apparently been withdrawn. FDA attorneys advised us that failure to remove the tolerances of these four drugs from the regulations was inadvertent, and that FDA does not establish tolerances for residues in milk of drugs that are not approved for use in dairy cows.

FDA's Center for Veterinary Medicine has established guidelines for veterinarians to 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. In establishing this policy, known as the extra-label drug use policy, FDA said that it would ordinarily refrain from initiating regulatory action against licensed veterinarians for using or prescribing in their practice any drugs they could legally obtain, provided

- a careful medical diagnosis was made by an attending veterinarian within the context of a valid veterinarian-client-patient relationship;
- a determination was made that: (a) there is no approved drug specifically labeled to treat the condition diagnosed or (b) drug therapy at the dosage recommended by the labeling has been found clinically ineffective in the animals treated;
- procedures are instituted to assure that the identity of the treated animals is carefully maintained; and
- the time period for drug withdrawal prior to marketing meat, milk, or eggs is significantly extended; steps are taken to assure that the assigned time frames are met; and no illegal residues occur.

FDA's extra-label use policy does not permit non-veterinarians, such as dairymen, to treat food-producing animals with drugs not approved for them and/or in an unapproved manner. FDA's policy states that lay persons cannot be expected to have sufficient knowledge and understanding concerning animal diseases, pharmacology, toxicology, drug interactions, and other scientific considerations to use drugs in treating food-producing animals in any manner other than as labeled on an approved drug.

FDA has declared that chloramphenicol and diethylstilbestrol may not be used in treating food-producing animals under the extra-label use policy. In addition, dimetridazole, ipronidazole, or other nitroimidazoles may not be used under the extra-label use policy in unapproved species. Furthermore, FDA has required manufacturers of all SMZ products to add a warning to product labels that SMZ is not to be used in female dairy cattle 20 months of age or older.

Monitoring Milk Safety

FDA administers the Federal/State Milk Sanitation Program through Interstate Milk Shippers Agreements to ensure the safety and wholesomeness of fresh milk and cream in the United States. Under this program, the producers of Grade A pasteurized milk are required to pass inspections and be rated by cooperating state agencies.

FDA's milk safety program is a collaborative federal/state effort that dates back to the mid-1920s. The program was established after the promulgation of the Standard Milk Ordinance by the Public Health Service to assist states and municipalities in initiating and maintaining effective programs for the prevention of milk-borne diseases.

To provide for uniform interpretation of this ordinance, an accompanying code was published in 1927 which set forth administrative and technical details to achieve satisfactory compliance. This milk regulation, now titled the Grade A Pasteurized Milk Ordinance (the Milk Ordinance), has undergone numerous revisions since that time and is the basic standard used today in the voluntary cooperative interstate milk safety program in which all 50 states and the District of Columbia participate. The Milk Ordinance is recognized by public health agencies, the milk industry, and many others as a national standard for milk sanitation.

Under the cooperative federal/state milk safety program, FDA does not routinely analyze milk samples for animal drug residues. Instead, FDA relies on the states to do routine testing of the milk supply. Milk processors also routinely test raw milk. FDA does not routinely review state or processor test results, but has conducted sampling and testing for pesticide chemicals, microbiological contaminants, and certain drug residues based on inspection findings or reports of potential problems.

Within the FDA, the administration of the agency's milk safety program is basically divided between the Center for Food Safety and Applied Nutrition (CFSAN) and CVM, with FDA's field offices performing inspections and sample collections and providing analytical support. CFSAN's Milk Safety Branch is responsible for monitoring the overall conduct of the milk safety program carried out by the states. CVM is responsible for providing technical expertise in the development of testing and analytical methodology related to animal drugs. In addition, CVM is responsible for evaluating the safety and effectiveness of new animal drugs and, with respect to new animal drugs for dairy cows, evaluating the conditions for use that would preclude the presence of potentially hazardous residues in milk.

Results and Limitations of FDA's Efforts to Determine the Presence of Antibiotic Drug Residues in the Nation's Milk Supply

FDA conducted several efforts to determine the presence of antibiotic drug residues in the nation's milk supply between 1988 and 1990, including:

- In March 1988, FDA conducted a survey of 10 cities to determine the presence of sulfamethazine, a suspected carcinogen (cancer-causing agent), in milk.
- Following the 1988 survey, FDA used data from a questionnaire sent to state regulatory agencies by the National Conference on Interstate Milk Shipments to determine whether the presence of SMZ in milk declined between May 1988 and September 1988, following FDA's efforts intended to eliminate SMZ use in milk-producing dairy cows (dairy cows).
- In late 1989 and early 1990, FDA conducted a survey of 14 cities to determine the presence of selected antibiotic drug residues in the milk supply after two independent surveys reported finding numerous contaminated milk samples.

Although similar in purpose, each of FDA's efforts were different in design and produced different results. In addition, limitations in FDA's efforts, both individually and collectively, may preclude any comparisons of the results of the efforts and any conclusions about the safety of the overall milk supply.

1988 Survey

In 1987 and 1988, laboratory milk tests performed by independent researchers detected the residues of a variety of animal drugs in milk. Among the drug residues reportedly detected was SMZ, one of about 45 antibiotic drugs in the class of drugs known as sulfonamides (sulfa). SMZ use in animals has been controversial because it is a suspected carcinogen. In addition, SMZ residues in milk may pose a risk for individuals allergic to sulfa-based drugs.

Although SMZ was not approved for use in milk-producing dairy cows and FDA had not established tolerances for SMZ residues in milk, FDA established an unofficial concern level for SMZ at 10 ppb in milk. Subsequent to reports that independent surveys had detected SMZ in milk, FDA, in March 1988, conducted its own milk survey related to the presence of SMZ.

Methodology

FDA regional office personnel collected five retail shelf milk samples (representing five different dairy processors) from each of 10 cities

(Atlanta, Boston, Chicago, Dallas, Denver, Kansas City, Newark, Philadelphia, San Francisco, and Seattle). FDA scientists initially used a test method, known as high pressure liquid chromatography (HPLC), to screen a total of 49 samples (one location provided only four samples) for SMZ. FDA scientists used a second, more specific method, known as mass spectrometry, to confirm the presence of SMZ in the samples that yielded positive results over 10 ppb under the HPLC method.

Results

The March 1988 survey found varying levels of SMZ in 73 percent of the samples tested. Specifically, 36 of the 49 samples tested showed levels of SMZ present in the milk ranging from 0.8 ppb to 40.3 ppb. Five samples tested above 10 ppb, the unofficial concern level for SMZ that FDA was using at that time, and 10 of the samples tested above 5 ppb.

Limitations

The 1988 FDA survey was limited for several reasons. First, the survey focused only on one animal drug—SMZ. The survey did not determine whether any other unapproved drug residues were present in the milk samples although FDA officials believe that about 25 unapproved drugs, some of which may pose toxicological concerns to humans, might be used in the dairy industry. The survey also did not determine whether any approved drugs were present at levels above their tolerances. Second, FDA did not design the survey to provide any statistically valid estimates from the survey results to the nation's milk supply. Thus, no conclusions can be reached on the basis of this limited survey regarding the safety of the nation's milk supply.

1988 Follow-Up Survey

The March 1988 survey results raised FDA's concern about the possible misuse of SMZ by the dairy industry because SMZ was not approved for use in dairy cows. In response, FDA took several steps to eliminate SMZ residues in the milk supply, including an educational campaign aimed at dairy farmers. FDA coordinated this educational effort with the National Conference on Interstate Milk Shipments (the National Conference)—a voluntary organization comprised of federal and state health and agricultural officials and the dairy industry—that together with FDA, oversees a cooperative, federal/state program (the Interstate Milk Shippers Program) to ensure the sanitary quality of milk and milk products shipped interstate.

To assess the effectiveness of the educational program and follow-up on the 1988 FDA survey, the National Conference sent a questionnaire on

October 8, 1988, to all state regulatory agency laboratories to obtain information regarding the number of raw milk samples tested for SMZ from May 1988 to September 1988 and the results of those tests. FDA's Milk Safety Branch analyzed the results.

Results

FDA's analysis of state data showed that 4,887 samples of raw milk were tested from May to September 1988 and that 5 percent of the reported samples tested (247 out of 4,887) contained SMZ. Further, FDA reported that only 1 percent of the reported test samples (54 out of 4,887) contained SMZ residues above 10 ppb. According to FDA, the results of the follow-up questionnaire indicated a significant reduction in the presence of SMZ residues in milk. On the basis of these results, FDA declared that the SMZ problem had been resolved.

Limitations

Although FDA concluded that the results from the follow-up survey showed a dramatic decrease in the level of SMZ residues in the nation's milk supply compared with the 1988 FDA survey results, limitations in the follow-up survey preclude direct comparison with FDA's 1988 survey or any conclusions regarding the safety of the nation's milk supply.

The follow-up survey cannot be relied upon to be representative of the nation's milk supply. First, the states responding to the survey who tested milk samples produce only about 65 percent of the nation's milk supply. More importantly, FDA could not provide documentation showing how the responding states sampled milk products. If the testing states did not use statistical methods to select the samples, then the resulting state and national data are highly suspect. FDA also did not know whether similar analytical methods and calibration standards were employed by the states in testing for SMZ residues, or whether all the methods used were capable of detecting SMZ at the 10 ppb health concern level FDA had established at that time.

In particular, some states may have used a method that is unable to detect many drug residues, including SMZ, at their levels of concern. Under the Pasteurized Milk Ordinance, the Bacillus Stearothermophilus disk assay is the only official method recognized to detect antibiotic drug residues in milk for regulatory purposes. However, FDA scientists have found that this method is primarily useful only in detecting penicillin antibiotics and cannot detect low levels of many other antibiotics. For example, the method can only detect levels of SMZ at and above 15

parts-per-million (ppm) or higher—1,500 times the 10 ppb concern level set by FDA for SMZ in milk.

Although FDA officials believe that states had other testing methods available in addition to the disk assay method to detect SMZ residues, it is unknown what specific methods the states used. If some states used only the disk assay method, then their results might have understated the number of samples containing SMZ residues above FDA's level of concern. Also, similar to the earlier 1988 survey, the 1988 follow-up effort only obtained data on the presence of SMZ—no data on the possible presence of other unapproved or approved drugs was gathered.

We cannot say with certainty that the results developed by FDA in its follow-up survey are flawed. However, given a sample representing only 65 percent of the nation's milk supply, no assurances that state samples were statistically drawn, and questions about state testing comparability, the results would likely be correct only by coincidence.

1990 Survey

Subsequent to FDA concluding, on the basis of the 1988 follow-up survey, that the SMZ problem had been solved, the Wall Street Journal (the Journal) reported the results of two surveys of animal drug residues in milk on December 29, 1989. One survey was sponsored by the Journal and the other by the Center for Science in the Public Interest (CSPI), a consumer food safety and nutrition organization.

The Journal reported that its survey found that 38 percent of 50 retail milk samples contained residues of antibiotics, possibly including SMZ and other unapproved drugs. The CSPI survey found that 20 percent of 20 retail milk samples collected in the Washington, D.C., area contained sulfa drugs, again possibly including SMZ and other unapproved drugs. Both surveys used an analytical method called Charm II.

The Charm II test is considered a screening test because it can reportedly detect the presence of seven classes of antibiotic drug residues in milk (e.g., aminoglycosides, beta-lactams (penicillins), chloramphenicol, macrolides, novobiocin, sulfonamides, and tetracyclines). However, except for chloramphenicol and novobiocin, which are individual chemical entities, the Charm II test can only indicate that a member of a particular chemical family of antibiotics may be present in milk samples tested, it cannot identify the specific antibiotic drug residue(s) responsible for the positive result. The identification of the specific antibiotic drug(s) must be determined by an independent confirmatory method of

analysis, according to FDA officials. For example, the Charm II test can indicate that a member of the sulfonamide class of antibiotics may be present in a milk sample tested, but cannot identify which specific sulfonamide drug(s), such as sulfamethazine or sulfadimethoxine, caused the positive response.

Methodology

FDA designed its 1990 survey to test the reliability of the independent surveys and to confirm or discount claims that animal drug residues are present in milk. To do this, FDA field office personnel obtained two containers of milk with the same lot number and date from 5 stores in each of 14 cities. The 14 cities included all those in the Journal's survey, as well as those included in FDA's previous survey efforts (Atlanta, Baltimore, Boston, Chicago, Dallas, Denver, Kansas City, Los Angeles, Miami, Minneapolis, New York, Philadelphia, San Francisco, and Seattle). The milk samples collected were then analyzed for the presence of antibiotic drug residues. According to FDA officials, the survey was a "snapshot" of the presence of certain drug residues in milk.

The containers collected at each location were shipped over night; one container was sent to FDA's Beltsville laboratory and one container was sent to FDA's Philadelphia District laboratory. Beltsville and Philadelphia ultimately received 70 milk samples each—1 container each from the five stores selected in each of the 14 cities. The Philadelphia laboratory used the same Charm II test method used in the Journal and CSPI surveys to screen its 70 milk samples for drug residues. Subsamples of all samples found positive by the Charm II test in Philadelphia were sent to FDA's Denver laboratory for further testing using modified HPLC, thin layer chromatography, gas chromatography, and microbiological test methodologies. Denver also performed mass spectrometry confirmatory testing for samples showing positive screening results for chloramphenicol, sulfadiazine, and sulfamethazine.

FDA officials believe that the mass spectrometry method, which is more difficult and costly to perform than other methods, represents state-of-the-art procedures in analytical chemistry and is the most reliable method available for identifying specific compounds. FDA considers all other test methods, including HPLC, to be screening tests because although they may be able to tentatively identify which one of a number of drugs may be present in milk, they cannot positively identify the drug found.

The Beltsville laboratory used multi-residue HPLC screening methods to test all of its 70 samples for the presence of 10 sulfa and 3 tetracycline antibiotic drugs. The Beltsville laboratory also used mass spectrometry to confirm and "fingerprint" the results of their HPLC testing, but only had confirmatory tests for chlortetracycline, oxytetracycline, sulfadiazine, sulfamethazine, and tetracycline. Also, with the exception of three sulfamethazine samples, Beltsville limited its confirmatory testing to samples that its HPLC testing indicated had residues equal to or in excess of established concern levels.

Overall, FDA could only perform confirmatory testing for six of the antibiotics selected for the 1990 survey, and, according to the Director of FDA's Center for Veterinary Medicine, the survey cost $350,000.

Results

In total, the screening test results from FDA's three participating laboratories initially indicated that 91 percent of the milk samples tested (64 out of 70) contained low levels of antibiotic drug residues and that many samples contained multiple drug residues. FDA performed mass spectrometry testing on three of the samples for which screening tests indicated low levels of sulfamethazine and confirmed its presence below 5 ppb. FDA did not find any antibiotic drug residues at or above concern levels, or at or above the level of detection sensitivity of the methods used on the remaining samples selected for mass spectrometry testing. However, FDA's attempt to confirm the presence of sulfachloropyridazine was inconclusive because of problems with the confirmatory method. FDA only had confirmatory methods for six of the other drugs selected for the 1990 survey, and three of these methods could not detect their respective drugs at established concern levels.

Philadelphia/Charm II Results

The Philadelphia laboratory's results using the Charm II test were similar to the results from the Journal and CSPI surveys in that many of the samples tested indicated the presence of antibiotic drugs. The Philadelphia laboratory results indicated that 51 percent (36 out of 70) of the samples contained antibiotic drug residues, mostly tetracyclines, and some samples contained multiple residues. Table II.1 provides a summary of FDA Charm II results.

Table II.1: FDA Screening Results for Drug Family Residues in the 1990 Milk Survey Using the Charm II Test

Drug Family	Number of Positive Samples Found	Percent of Positive Samples Found (out of 70)
Aminoglycosides (gentamicin)	4	6
Beta-lactams (penicillin)	1	1
Chloramphenicol	1	1
Macrolides (erythromycin)	1	1
Novobiocin	5	7
Sulfonamides	15	21
Tetracyclines	34	49

Source: Prepared by GAO from FDA data.

Denver Laboratory Results

Subsamples of the 36 samples found positive using the Charm II test were sent to FDA's Denver laboratory for further screening and confirmatory testing. Based on this screening and/or confirmatory testing, the Denver laboratory reported that it could not corroborate any of the Philadelphia laboratory's positive Charm II results. However, the test method Denver used for five samples which Charm II indicated the presence of novobiocin was not as sensitive to the drug as the Charm II test is claimed to be. The Denver method was also incapable of detecting novobiocin residues at the health concern level established by FDA.

Beltsville Laboratory Sulfa Drug Results

The Beltsville laboratory's HPLC test results indicated that 86 percent (60 out of 70) of the milk samples tested contained sulfa drug residues; 46 percent (32 out 70) of the samples contained multiple sulfa residues. Specifically, Beltsville initially found that 16 percent (11 out of 70) contained sulfa residues greater than or equal to 10 ppb, the FDA-designated concern level for these drugs at that time; 83 percent (58 out of 70) contained sulfa residues at levels less than 5 ppb; and 1 percent (1 out of 70) contained residues between 5 and 10 ppb. Table II.2 provides a summary of initial results from the Beltsville laboratory using HPLC.

Table II.2: Initial FDA Screening Results for Sulfa Drug Residues in the 1990 Milk Survey Using HPLC

Drug	Number of Positive Samples Found	Percent of Positive Samples Found (out of 70)
Sulfachloropyridazine	3	4
Sulfadiazine	32	46
Sulfadimethoxine	3	4
Sulfamerazine	47	67
Sulfamethazine	10	14
Sulfamethizole	1	1

Source: Prepared by GAO from FDA data.

Beltsville's HPLC results also indicated that 10 of the 11 samples that tested positive for sulfa residues at or above 10 ppb contained sulfadiazine at levels ranging from 10 to 315 ppb and that 1 sample contained sulfachloropyridazine at 15 ppb.

However, the Beltsville laboratory did not confirm the presence of sulfadiazine at or above 10 ppb in any of the samples found positive by their HPLC method. Through additional testing using a revised HPLC procedure, thin layer chromatography, and mass spectrometry, Beltsville subsequently found that the compound theobromine interfered with the initial HPLC screening tests and led to false positive results. Theobromine is a caffeine-related substance found in chocolate. FDA believes that the substance may have found its way into the milk sampled as a trace residue of chocolate milk processed by the same dairy plants. (Beltsville did not reanalyze samples with low levels of sulfadiazine (less than 10 ppb) using the revised HPLC procedure because these levels were under the designated level of concern.) Beltsville attempted to confirm the presence of sulfachloropyridazine above 10 ppb in the remaining sample, but its analysis was inconclusive because of problems with the confirmatory method.

Although low levels of sulfa drugs (i.e., less than 5 ppb) were detected in many of the milk samples using the HPLC method, FDA advised that these results must be interpreted cautiously because many low level positive results could be due to interference near the ability of this method to detect low levels of sulfa drugs in milk. Also, Beltsville generally did not attempt to confirm HPLC results indicating sulfa residues below the concern level of 10 ppb. However, three samples with the highest indicated concentrations of SMZ (all less than 5 ppb) were analyzed using the mass

spectrometry method and the presence of SMZ[1] in these samples was confirmed.

Beltsville Laboratory Tetracycline Results

The Beltsville laboratory HPLC test results indicated that one sample tested contained oxytetracycline at 99 ppb. Beltsville was unable to confirm the presence of this drug using its mass spectrometry method. However, the confirmatory method could only detect oxytetracycline at 100 ppb or more. The health concern level FDA set for this drug was 30 ppb.

Limitations

As in its previous efforts, the 1990 FDA survey of antibiotic drug residues in milk was not statistically designed to be representative of the nation's milk supply. According to FDA officials, the survey was a snapshot and the results could be completely different if the same survey was conducted again. In addition, the 1990 survey was limited for several reasons.

Limited Number of Confirmatory Methods Available

FDA may have been unable to confirm some of the positive screening test results in its 1990 survey because it did not have methods to identify and confirm the presence of all drugs detected by the screening methods. Thus, unconfirmed results may have been due, in part, to the presence of a drug residue not detectable by FDA's confirmatory method.

For example, about 32 antibiotic drugs, approved and/or unapproved for use in dairy cows, may have been in use by the dairy industry at the time of the 1990 survey. However, other than the Charm II test, FDA only had screening tests of its own for 17 antibiotic drugs included in its 1990 survey and mass spectrometry methods to confirm the presence of only six of these drugs in the milk samples tested. Regarding sulfa antibiotics, the Charm II test FDA's Philadelphia laboratory used reportedly could, in its screening mode, detect 15 drugs in the sulfa class family. Only 10 sulfa drugs were included in the 1990 survey, and FDA had confirmatory (mass spectrometry) methods for only 2 of these.

In addition, the Beltsville laboratory found evidence of a substance present in milk samples collected from Philadelphia that did not correspond to any of the 10 sulfa drugs that its HPLC methods could identify. According to the Chief, Method Validations and Analytical Branch,

[1]During the 1990 survey, CVM revised its preliminary risk assessment for SMZ and concluded that it could not set a safe level of SMZ in milk because of data gaps, but estimated a safe concentration of total residues of SMZ (including metabolites) in milk to be 12 ppb, with a likely marker residue in the 1-5 ppb range.

Center for Veterinary Medicine, the presence of the identified substance could possibly be due to the processing and packaging of the retail milk samples used in the survey, the result of animal husbandry practices, or the presence of another sulfa or some other drug.

Discounted Results Questioned

FDA discounted Charm II test results from its Philadelphia laboratory that indicated the presence of novobiocin in 5 samples, or 7 percent of the 70 samples tested, based on the results of a microbiological screening test method used by its Denver laboratory that was less sensitive to the drug than the reported detection capability of Charm II. The microbiological method was also unable to detect novobiocin residues at the tolerance level established by FDA.

Specifically, using the Charm II test with a reported detection sensitivity of 50 ppb, the Philadelphia laboratory found five samples that contained novobiocin. Denver, using a "green book" microbiological screening test with a detection sensitivity of 200 ppb, did not corroborate these results. However, the tolerance level established by FDA for novobiocin was 100 ppb. According to FDA officials, there were no other screening tests available for novobiocin. Also, according to the Chief, Method Validations and Analytical Branch, Center for Veterinary Medicine, the Beltsville laboratory did not test milk samples for this drug because FDA lacked a confirmatory method for novobiocin. Consequently, although the Charm II results indicating the presence of novobiocin were discounted, FDA did not know whether novobiocin was present in the samples tested above the established tolerance level, but below the detection level of the green book method used.

Limitations in Existing Confirmatory Methods

Some of the other analytical methods FDA used in the 1990 survey were also unable to detect and confirm the presence or absence of various drug residues at their concern levels. For example, three of the six drugs in the 1990 survey for which FDA had confirmatory methods were tetracycline antibiotics. These three drugs were/are approved to treat dairy cows, but only one, chlortetracycline, had an FDA-established tolerance for its residue in milk. For survey purposes, FDA established unofficial concern levels for the residues of these three drugs in milk. However, the confirmatory methods FDA used in the 1990 survey were incapable of detecting the presence of these drugs at their concern levels. For example, the concern level for oxytetracycline was 30 ppb, but FDA's mass spectrometry confirmatory test could only confirm it at 100 ppb or more. Consequently, although the Beltsville laboratory found one sample that contained oxytetracycline at 99 ppb using the HPLC method,

Beltsville was unable to confirm the HPLC result with the mass spectrometry method.

Thus, although FDA reported that it could not confirm the presence of any tetracycline drugs, the drugs may still have been present at levels exceeding the concern level for human consumption, but below the confirmatory test level of detection for these drugs. Table II.3 shows a comparison between the tolerance/concern levels for the antibiotic drug residues in milk tested and the level of detection of testing methods FDA used in the 1990 survey.

Table II.3: Tolerances/Levels of Concern for Selected Antibiotic Drug Residues in Milk and the Level of Detection for the Methods FDA Used in Its 1990 Survey (In Parts-Per-Billion)

Drug	Tolerance/ Concern Level[a]	Philadelphia	Beltsville		Denver			
		Charm II[b]	BHPLC[c]	BMS[d]	DGBMB[e]	DHPLC[f]	DTLC[g]	DMS[h]
Penicillin	0/10	4.8[i]	•	•	10	•	•	•
Tetracycline	−/80	200[i]	50	100	50−175	40	•	•
Chlortetracycline	0/30	200[i]	30	100	50−175	40	•	•
Oxytetracycline	−/30	200[i]	40	100	50−175	40	•	•
Chloramphenicol	−/0	100	•	•	•	•	•	1
Streptomycin	0/125	100j	•	•	•	•	•	•
Gentamicin	−/30	50[j]	•	•	20−70	•	•	•
Erythromycin	0/50	100[i]	•	•	25	•	•	•
Novobiocin	100/−	50	•	•	200	•	•	•
Sulfanilamide	−/10	10[i]	5	•	•	•	•	•
Sulfadiazine	−/10	10[i]	0.9	10	•	•	100	10
Sulfathiazole	−/10	10[i]	1	•	•	•	50	•
Sulfamerazine	−/10	10[i]	0.5	•	•	•	10	•
Sulfapyridine	−/10	10[i]	0.9	•	•	•	•	•
Sulfamethizole	−/10	10[i]	2	•	•	•	•	•
Sulfamethazine	−/10	10[i]	2	2	•	•	5	5
Sulfachloropyridazine	−/10	10[i]	1	•	•	•	•	•
Sulfadimethoxine	10/10	10[i]	0.7	•	•	•	5	•
Sulfaquinoxaline	−/10	10[i]	1	•	•	•	10	•

[a]Value indicates tolerance and/or level of concern for drug residues in milk at the time of the FDA 1990 survey.

[b]Charm II = Values are for the screening mode of the Charm II test used by FDA's Philadelphia District Laboratory.

[c]BHPLC = High pressure liquid chromatography method that the FDA Beltsville Laboratory used.

[d]BMS = The mass spectrometry method that the Beltsville Laboratory used to confirm test results.

[e]DGBMB = FDA Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols, Revised Oct. 1968. Reprinted Dec. 1974. (Called the Green Book microbiology methods.)

[f]DHPLC = Modified HPLC method that the FDA Denver Laboratory used.

[g]DTLC = The thin layer chromatography method that the Denver laboratory used.

[h]DMS = The gas chromatography/mass spectrometry method that the Denver Laboratory used.

[i]The Charm II test generally detects the presence of antibiotic drug families—not individual drugs. The values given represent the levels of detection for the family of drugs for the individual drug listed.

[j]Different Charm II detection levels are given for gentamicin and streptomycin although both are members of the aminoglycoside family, because the manufacturer claims that the test is more sensitive to gentamicin.

Source: Prepared by GAO using FDA data.

In establishing concern levels for the 1990 survey, FDA could only consider parent drug compounds because they lacked data on the metabolites of the parent drug compounds in milk. Accordingly, FDA did not analyze the milk samples for metabolites of the antibiotic drugs they tested for—only the parent drug compound.

Unexplained Discrepancies in Results Exist

Several unexplained discrepancies in test results exist from the different methods that FDA used in its 1990 survey that may render the survey results inconclusive. For example, as indicated earlier in table II.1, most of the Charm II positive results were for tetracycline. However, the Denver laboratory was unable to corroborate these results using green book microbiological methods, even though these methods were reportedly more sensitive to tetracycline than Charm II. According to FDA, there are no data available to explain this difference. Similarly, the Beltsville laboratory was unable to detect three specific tetracyclines in most of the samples that Charm II found positive for tetracycline drugs, even though the HPLC method Beltsville used was reportedly more sensitive to these drugs than Charm II.

Validity of Test Methods

Questions exist about whether the methods FDA used in its 1990 survey had been adequately validated. The HPLC and mass spectrometry methods FDA used in the 1990 survey did not undergo multilaboratory evaluation as specified in the Center for Veterinary Medicine formal methods trial procedures. For example, the Center considers the HPLC method only a research method because it has not gone through the usual validation procedures normally followed in FDA. FDA officials said that the methods were validated at FDA's own laboratories and peer reviewed by two university scientists expert in toxicological analysis. Although the reviewers concluded that the manner in which FDA used its methods in the survey was credible and adequate, they could not fully "credentialize" the procedures because of the lack of data on the reproducibility of the methods. Furthermore, the scientists questioned the number of false positives produced by the Beltsville HPLC screening procedures.

In addition, two scientists from the Centers for Disease Control (CDC) evaluated FDA's analytical methods used in the 1990 survey and found them adequate. However, the CDC scientists suggested that additional method development work is needed to determine the performance of the methods using retail versus raw milk and to lower the level of detection for the methods below the concern levels for the tetracycline drugs tested.

For example, the analytical methods FDA used to detect the presence of the three tetracyclines were developed using raw milk. However, FDA collected milk samples off the shelf. The extent to which retail versus raw milk may affect test results is unknown.

Handling of Milk Samples Collected

Questions exist about FDA's quality assurance of the handling of the milk samples collected. About 45 percent of the milk samples analyzed in the 1990 survey were beyond their shelf-life "pull-by dates." According to FDA, milk conditions such as spoiled milk, can cause the Charm II test to indicate false positive results, especially for tetracyclines. Consequently, the selection and handling of milk samples are critical to achieving accurate results.

According to FDA officials, because of time constraints the 1990 survey was not structured and no criteria were set for what the pull-by dates for milk samples should have been. However, none of the samples analyzed by FDA were spoiled, according to the Chief, Method Validations and Analytical Branch, Center for Veterinary Medicine.

Objectives, Scope, and Methodology

As requested by the Chairman, Human Resources and Intergovernmental Relations Subcommittee, House Committee on Government Operations, we reviewed the adequacy of survey efforts conducted by FDA in 1988 and 1990 to determine the presence of animal drug residues in milk and whether the information developed provided sufficient basis for FDA's public statements attesting to the safety of the milk supply.

To obtain information on FDA's survey efforts, we interviewed officials and obtained documents from FDA's Center for Veterinary Medicine, Center for Food Safety and Applied Nutrition, Office of Regulatory Affairs, and the FDA laboratories at Beltsville, Denver, and Philadelphia. We also reviewed documents the Subcommittee obtained from FDA related to its surveys of animal drug residues in milk and pertinent reports FDA issued as a result of its surveys. In addition, we reviewed FDA, state, and industry testimony regarding their efforts to detect drug residues in milk, given before the Subcommittee on February 6, 1990. We also met with the Center for Science in the Public Interest, to determine its views of FDA's surveys of animal drug residues in milk.

Our review, which was done from April to September 1990, was conducted in accordance with generally accepted government auditing standards. We conducted our review primarily at FDA's CVM headquarters in Rockville, Maryland.

The information in this report was discussed with officials in FDA's Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, and Office of Regulatory Affairs. Where appropriate, changes have been made based on the discussion to further clarify the information presented. However, as your office requested, we did not obtain official agency comments on a draft of this report.

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