November 12, 2013

CVM Animal Health Hazard Evaluation Committee

Problem: Chicken Jerky Treats Containing Parts Per Billion Levels of Six Drugs
Recall Event ID/RES #: 64061
DAF/Surveillance #: 13084

Copy: CVM Recall and Emergency Coordinator (Kathy Hemming-Thompson), HFV-234

Field/RES Report Data:

Recalling firm:

Del Monte Foods Corp.
300 Clay Street
San Francisco, California 94111-3403 United States
Phone: 415-442-5300
FEI # (b) (4)

Alternate Address:
Milo's Kitchen LLC (a subsidiary of Del Monte Foods)
One Maritime Plaza
San Francisco, CA 94111

Manufacturer:

(b) (4)

Products & Codes (Formula):

- All sizes of Milo's Kitchen brand Home-Style Dog Treats—Chicken Jerky

  3.3 oz. Universal Product Code (UPC) 0-79100-50471-8

  14 oz. UPC 0-79100-51077-1

  20 oz. UPC 0-79100-50468-8

- All sizes of Milo's Kitchen brand Chicken Grillers Home-Style Dog Treats—Chicken Recipe with natural smoked flavor

  3.3 oz. UPC 0-79100-51310-9

  14 oz. UPC 0-79100-51312-3

  20 oz. UPC 0-79100-51313-0

Quantity Distributed:

The Chinese manufacturer produced (b) (4) cases of Chicken Jerky and (b) (4) cases of Chicken Grillers for a total of (b) (4) cases. (b) (4) cases of chicken jerky and (b) (4) cases of chicken grillers for a total of (b) (4) cases were shipped internationally ((b) (4)) by the Chinese manufacturer.

Quantity Returned:

The recall letter dated January 8, 2013 from Milo's Kitchen (Tim Cole, EVP Sales) asks each customer of the recalling firm (presumably (b) (4) distributors, (b) (4) retailers and (b) (4) military installations with the Dept. of Defense) to remove all sizes and lot numbers of the 2 products (Chicken Jerky and Chicken Grillers) from their shelves and destroy it via their reclamation process. The recall letter and/or press release also indicates that each customer should work with their Del Monte customer service representative to return full pallet quantities of the affected product and that consumers who discard the treats will receive a full refund.

No information was provided on the quantity of the two products (Chicken Jerky and Chicken Grillers) that was returned to Del Monte, destroyed by the customer's reclamation process, or discarded by consumers.

The recall is not for specific lot numbers, but for all products currently in commerce. No information was provided on all the lot numbers affected by this recall. However, assuming the use-by-date is ~18 months (~78 weeks) from the date the product was ordered, assuming the packaging date is (b) (4) after the product is ordered, assuming it takes about (b) (4) (b) (4) to ship the packaged dog treats from the manufacturer in China to the (b) (4) and then from the (b) (4) to the US, assuming all the packaged dog treats en route to the US at the time of the recall never made it into domestic commerce in the US, assuming this recall effectively went down to the consumer level, assuming all out-of-date product had previously been removed from retail and dog owner shelves and destroyed, and assuming all manufacturing in China of the 2 recalled products destined for the USA stopped on January 9, 2013, then this recall likely affected all uneaten Milo's Kitchen Chicken Jerky and Chicken Grillers that were destined for the US and packaged by (b) (4) from about July 16, 2011 (where the first 6 numbers and letters of the lot number would be 1197HV) to January 9, 2013 (where the first 6 numbers and letters of the lot number would be 3009HV) (see background section for details about the lot numbers). Since all lots had HV in the fifth and sixth position of the lot number, this recall likely affected lots with the following range in the first 4 numbers -- 1197 to 1365 and 2001 to 2366 and 3001 to 3009.

Recall Contact:

Mike Hayes
Director – Food Safety and Quality
Milo's Kitchen LLC
375 North Shore Drive
Pittsburgh, Pennsylvania 15212 USA
Telephone: (412) 222-8420

Public Contact

Tim Cole
EVP, Sales
Del Monte Foods Corp.
300 Clay Street
San Francisco, California 94111-3403 USA
Telephone: 877-228-6493

FDA District:
San Francisco

Field Recommended Classification:
Class III

Effectiveness Check Level:
Check Level A or 100%

Audit Check Level:
Check Level D or 2%

Background:

On January 7, 2013, the State of New York Department of Agriculture and Markets (SNYDAM) informed the U.S. Food and Drug Administration (FDA) and the recalling firm that parts per billion (ppb) levels of six drugs had been found in 5 samples of Milo's Kitchen Chicken Jerky.

Three of these samples (FL-56427, FL-56428 and FL-59345) were collected on November 28, 2012 by Inspectors from SNYDAM. These 3 samples were collected off the shelf at Petco in Albany, NY (samples FL-56427 and FL-456428) and at Petsmart in Syracuse, NY (sample FL-59345). These 3 samples had best if used by dates of 05 10 13 (May 10, 2013), of 05 15 13 (May 15, 2013) and of 02 22 14 (February 22, 2014), respectively. These 3 samples had lot numbers of 1320HVC, 1325HVC, and 2243HVB, respectively. The first digit of the lot number indicates (b) (4) . The second through fourth digits provide the (b) (4) .

These 3 samples were analyzed by the SNYDAM Food Laboratory (FL) for six drugs –

sulfaquinoxaline [misspelled as sulfaquinoxyline on the sampling and analysis report],
sulfaclozine [equivalent to sulfachloropyrazine],
sulfamethoxazole,
tilmicosin,
trimethoprim, and
enrofloxacin.

The collection and analysis of these 3 samples were paid for by the SNYDAM. The analytical results for these 3 samples were finalized on January 3, 2013.

Earlier in 2012, the SNYDAM collected and analyzed 2 samples of Milo's Kitchen Chicken Jerky under a contract with the FDA. One sample (FL-59614) was collected by a SNYDAM Inspector on March 9, 2012 off the shelf at Shop-Rite Supermarkets in Monticello, NY. It had a best if used by date of 03 23 13 (March 23, 2013) and a lot number of 1272HVA. The other sample (FL-58886) was collected by a SNYDAM Inspector on April 5, 2012 off the shelf at Wal-Mart in Lancaster, NY. It had a best if used by date of 04 24 13 (April 24, 2013) and a lot number of 1304HVC.

These 2 samples were analyzed by the SNYDAM FL for five drugs –

sulfaquinoxaline [misspelled as sulfaquinoxyline on the sampling and analysis report],
sulfaclozine [equivalent to sulfachloropyrazine],
tilmicosin,
trimethoprim, and
enrofloxacin.

The analytical results for these 2 samples that were collected and analyzed by SNYDAM under a contract with the FDA (paid for by the FDA) were finalized on January 4, 2013.

The reported analytical results for these 5 samples are provided in Appendix A (pages 1 - 5) (see attached Excel document). In 4 of the 5 samples, 10 subsamples were analyzed. In 1 of the 5 samples (FL-58886), 23 subsamples were analyzed. The results from each subsample are provided and all the reported values were not corrected for recovery.

DRUGS NOT PRESENT AT QUANTIFIABLE LEVELS

Sulfamethoxazole. The 3 samples collected by SNYDAM that were not part of a FDA contract were analyzed for sulfamethoxazole. The 2 samples collected under FDA contract were not. Overall, 30 subsamples were analyzed for sulfamethoxazole and in 29 subsamples (96.7%) the levels were reported as non-detectable (<1.0 ppb). One subsample (3.3%) was found to contain sulfamethoxazole in trace amounts (≥1.0 ppb, the limit of detection [LOD], but <3.0 ppb, the limit of quantification [LOQ]). No subsample (0.0%) contained quantifiable levels of sulfamethoxazole (≥3.0 ppb).

Trimethoprim. All 5 samples (63 subsamples) were analyzed for trimethoprim and 62 subsamples (98.4%) were found to contain non-detectable (<1.0 ppb) levels. One subsample (1.6%) was found to contain trimethoprim in trace amounts (≥1.0 ppb, the LOD, but <3.0 ppb, the LOQ). No subsample (0.0%) contained quantifiable levels of trimethoprim (≥3.0 ppb).

Since no quantifiable levels of sulfamethoxazole or trimethoprim were found in all subsamples tested (n=30 and 63, respectively), these 2 drugs are not likely the cause of the adverse events reported to FDA/CVM by pet owners while feeding their dogs Milo's Kitchen Chicken Jerky.

DRUGS PRESENT AT QUANTIFIABLE LEVELS IN <10% OF SUBSAMPLES

Enrofloxacin. All 5 samples (63 subsamples) were analyzed for enrofloxacin and 53 subsamples (84.1%) were found to contain non-detectable (<1.0 ppb) levels. Nine subsamples (14.3%) were found to contain enrofloxacin in trace amounts (≥1.0 ppb, the LOD, but <3.0 ppb the LOQ). Only 1 subsample (1.6%) contained quantifiable levels of enrofloxacin (≥3.0 ppb) and the level found was 14 ppb, which is just above the LOQ.

Tilmicosin. All 5 samples (63 subsamples) were analyzed for tilmicosin and 54 subsamples (85.7%) were found to contain non-detectable (<1.0 ppb) levels. Five subsamples (7.9%) were found to contain tilmicosin in trace amounts (≥1.0 ppb, the LOD, but <3.0 ppb, the LOQ). Only 4 subsamples (6.3%) contained quantifiable levels of tilmicosin (≥3.0 ppb) and the levels found were just above the LOQ (6.37 ppb, 6.40 ppb, 6.75 ppb and 25 ppb).

Since quantifiable levels of tilmicosin and enrofloxacin were found in only 1 of 63 and 4 of 63 subsamples, respectively, and since the quantifiable levels found were reported as at or below 25 ppb, these 2 drugs are not likely the cause of the adverse events reported to FDA/CVM by pet owners while feeding their dogs Milo's Kitchen Chicken Jerky.

Although tilmicosin is not approved for use in chickens in the US, this drug has tolerances well above 25 ppb in edible tissues of other food animal species. For instance, the tolerance for tilmicosin is 0.1 parts per million (ppm) (0.1 ppm is equivalent to 100 ppb) in the muscle of cattle, sheep and swine. Tilmicosin also has a tolerance in the liver of cattle and sheep of 1.2 ppm (1,200 ppb) and a tolerance of 7.5 ppm (7,500 ppb) in the liver of swine. All these tolerances are listed in 21 CFR 556.735 (Title 21 of the Code of Federal Regulations, part 556, section 735).

Although enrofloxacin is not approved for use in chickens in the US, this drug has a tolerance well above 14 ppb in edible tissue of swine. The tolerance for enrofloxacin, which is listed in 21 CFR 556.226, is 0.5 ppm in the liver of swine (0.5 ppm is equivalent to 500 ppb).

DRUGS PRESENT AT QUANTIFIABLE LEVELS IN ≥ 33% OF SUBSAMPLES

Sulfaclozine. All 5 samples (63 subsamples) were analyzed for sulfaclozine and 11 subsamples (17.5%) were found to contain non-detectable (<1.0 ppb) levels. Twelve subsamples (19.0%) were found to contain sulfaclozine in trace amounts (≥1.0 ppb, the LOD, but <3.0 ppb, the LOQ). Forty subsamples (63.5%) contained quantifiable levels of sulfaclozine (≥3.0 ppb). The levels ranged between 3.4 and 751 ppb, and were distributed as follows:

3.0 to 15.0 ppb = 27 subsamples (42.9% of all subsamples tested)
15.1 to 85.0 ppb = 7 subsamples (11.1% of all subsamples tested)
85.1 to 340.0 ppb = 3 subsamples (4.8% of all subsamples tested)
340.1 to 1,000 ppb = 3 subsamples (4.8% of all subsamples tested)

Sulfaquinoxaline. All 5 samples (63 subsamples) were analyzed for sulfaquinoxaline and 19 subsamples (30.2%) were found to contain non-detectable (<1.0 ppb) levels. Twenty-three subsamples (36.5%) were found to contain sulfaquinoxaline in trace amounts (≥1.0 ppb, the LOD, but <3.0 ppb, the LOQ). Twenty-one subsamples (33.3%) contained quantifiable levels of sulfaquinoxaline (≥3.0 ppb). The levels ranged between 3.0 and 828 ppb, and were distributed as follows:

3.0 to 15.0 ppb = 15 subsamples (23.8% of all subsamples tested)
15.1 to 85.0 ppb = 3 subsamples (4.8% of all subsamples tested)
85.1 to 340.0 ppb = 1 subsample (1.6% of all subsamples tested)
340.1 to 1,000 ppb = 2 subsamples (3.2% of all subsamples tested)

Quantifiable levels of sulfaclozine (which is equivalent to sulfachloropyrazine) and sulfaquinoxaline were found in 40 of 63 and 21 of 63 subsamples, respectively. In the 40 subsamples with quantifiable levels of sulfaclozine, 27 (67.5%) were between 3.0 – 15.0 ppb, just above the LOQ, and 34 (85.0%) were above the LOQ (>3.0 ppb), but at or below 85.0 ppb. In the 21 subsamples with quantifiable levels of sulfaquinoxaline, 15 (71.4%) were between 3.0 – 15.0 ppb, just above the LOQ, and 18 (85.7%) were above the LOQ (>3.0 ppb), but at or below 85.0 ppb. Even though at least 85% of the time the quantifiable residues of these 2 drugs were reported as less than or equal to 85.0 ppb and slightly more than two-thirds of all quantifiable levels were just above the LOQ (between 3.0 – 15.0 ppb), further discussion of these sulfaclozine and sulfaquinoxaline residues is warranted because dogs appear to be sensitive to several different sulfonamide drugs following oral administration. The topic of sulfonamide sensitivity in dogs and humans from non-FDA sources will be discussed later under the heading of Overview of Adverse Reactions to Sulfonamide Drugs in Dogs and Other Animals and in Humans from Non-FDA Sources. Some of the FDA data on adverse reactions to sulfonamide drugs in dogs will also be presented later, but first additional information on the following three topics will be provided.

a) FDA approved uses and tolerances in chickens for sulfaclozine and sulfaquinoxaline.
b) Tolerances for all sulfonamide drugs in 21 CFR 556
c) Negligible residues

FDA APPROVED USES AND TOLERANCES IN CHICKENS FOR SULFACLOZINE AND SULFAQUINOXALINE

See Appendix B, which is an attached Microsoft Word document, for details.

TOLERANCES FOR ALL SULFONAMIDE DRUGS IN 21 CFR 556

A summary of all the tolerances for sulfonamide drugs in 21 CFR 556 is presented below:

Sulfonamide drugs with a tolerance of 0.1 part per million (or 100 ppb) for negligible residues in uncooked edible tissues of various animals in 21 CFR 556 include the following:

a) sulfabromomethazine sodium (cattle) (21 CFR 556.620)
b) sulfachlorpyridazine (calves and swine) (21 CFR 556.630)
c) sulfadimethoxine (chickens, turkeys, cattle, ducks, salmonids, catfish and chukar partridges (21 CFR 556.640)
d) sulfaethoxypyridazine (cattle) (21 CFR 556.650)
e) sulfamethazine (chickens, turkeys, cattle and swine) (21 CFR 556.670)
f) sulfaquinoxaline (chickens, turkeys, calves and cattle) (21 CFR 556.685)
g) sulfathiazole (swine) (21 CFR 556.690)

Sulfonamide drugs with a tolerance of zero for residues in uncooked edible tissues of animals and/or milk in 21 CFR 556 include the following:

a) sodium sulfachloropyrazine monohydrate (chickens) (21 CFR 556.625)
b) sulfaethoxypyridazine (swine and milk) (21 CFR 556.650)
c) sulfamerazine (trout) (21 CFR 556.660)

NEGLIGIBLE RESIDUES: FDA AND EPA

The background information below on negligible residues came verbatim from a draft preamble being prepared by Dr. Cathie Marshall and other scientists at FDA/CVM in early 2013.

"FDA's human food safety evaluation of residues of new animal drugs has evolved over the past 50 years. Before the mid-1970's, FDA based tolerances primarily on a small number of toxicity studies, typically 90-day feeding studies in laboratory animals. From the results of these studies, FDA determined the "no-observed-effect-level" (NOEL). The acceptable daily intake (ADI) for total residue of a drug was calculated by dividing the NOEL by the appropriate safety factor to adjust for the differences between test animals and humans. To calculate the safe concentrations, FDA considered food consumption values and human body weight. Consumption was estimated as a total dietary exposure of 1500 grams of food per day. Historically, FDA used an average human weight of 50 or 60 kilograms (kg). Because these toxicology studies did not assess lifetime effects (which could only be observed in long-term feeding studies), FDA applied a 2000-fold safety factor to the NOELs. FDA generally sets the tolerance for "negligible" residues of these drugs at 0.1 part per million (ppm) in muscle and 10 parts per billion (ppb) in milk, even if the computed tolerance exceeded the calculated values."

The EPA's definition for negligible residues is found in 40 CFR 180.1 (j), is provided verbatim below, and appears similar to the FDA's discussion on this topic above.

"The term negligible residue means any amount of a pesticide chemical remaining in or on a raw agricultural commodity or group of raw agricultural commodities that would result in a daily intake regarded as toxicologically insignificant on the basis of scientific judgment of adequate safety data. Ordinarily this will add to the diet an amount which will be less than 1/2,000th of the amount that has been demonstrated to have no effect from feeding studies on the most sensitive animal species tested. Such toxicity studies shall usually include at least 90-day feeding studies in two species of mammals."

OVERVIEW OF ADVERSE REACTIONS TO SULFONAMIDE DRUGS IN DOGS AND OTHER ANIMALS AND IN HUMANS FROM NON-FDA SOURCES

Published Information

Dogs and Other Animals

The following information comes directly from Chapter 39 Sulfonamides (written by Jerry W. Spoo and Jim E. Riviere) on pages 757-758 (Pharmacokinetics of Sulfonamides section, Toxicity sub-section) in the 7th Edition of Veterinary Pharmacology and Therapeutics (1995; edited by H. Richard Adams; Iowa State University Press / Ames).

"Sulfonamide-induced toxicoses may be classified as nonimmunologic or immunologic in etiology. Of the immunologic sulfonamide-induced toxicoses, most have been documented in the canine."

"Several cases of sulfonamide-induced KCS [keratoconjunctivitis sicca] have been reported in dogs treated with sulfasalazine, sulfadiazine, and sulfamethoxazole…Sulfonamide-induced KCS does not seem to affect any particular breed of dog, and the precise mechanism behind the induction of KCS is not known; however, it is believed to be the result of a hypersensitivity reaction…"

"Hypoprothrombinemia has been reported in dogs…, in coyote pups…, and in Leghorn chickens given sulfaquinoxaline…Sulfaquinoxaline is not an anticoagulant in vitro, nor does it destroy or otherwise inactivate prothrombin. Nevertheless, recent studies have reported that sulfaquinoxaline is a potent inhibitor of vitamin K epoxide reductase, and this inhibition is the most likely reason for the hypothrombinemic reaction seen in the reported cases of sulfaquinoxaline toxicosis. Treatment is by vitamin K_1 administration for 4-7 days, and recovery is uneventful."

"Aplastic anemia presumably induced by drug therapy with trimethoprim-sulfadiazine has been reported…Thrombocytopenia has been reported in animals and in humans…The thrombocytopenia in animals, as in humans, is probably associated with an immune-mediated component that may resolve after the drug is discontinued."

"Other idiosyncratic reactions have been reported in dogs…These reactions include polyarthritis and fever…cutaneous eruptions, and hepatitis…all believed to be linked to an immunologic component. Some less commonly used sulfonamides have been linked to hypoglycemia in ducks and dogs…Sulfonamides are also known to interfere with thyroid hormone synthesis by blocking the conversion of iodide to iodine and may increase thyroid releasing hormone or thyroid stimulating hormone."

Humans

The following statements related to adverse reactions in humans come directly from the Adverse Effects and Treatment section under Sulphamethoxazole on pages 280-281 in the Chapter on Antibacterial Agents (pages 129-297) in the thirty-first edition (1996) of MARTINDALE The Extra Pharmacopoeia (edited by James E F Reynolds; London; Royal Pharmaceutical Society).

"Nausea, vomiting, anorexia, and diarrhoea are relatively common following administration of sulphamethoxazole and other sulfonamides."

"Hypersensitivity reactions to sulphonamides have proved a problem. Fever is relatively common, and reactions involving the skin may include rashes, photosensitivity reactions, exfoliative dermatitis…Dermatitis may occur on contact of sulphonamides with the skin…"

"Nephrotoxic reactions including interstitial nephritis and tubular necrosis, which may result in renal failure, have been attributed to hypersensitivity to sulphamethoxazole…"

"Blood disorders have occasionally occurred during treatment with the sulphonamides including sulphamethoxazole, and include agranulocytosis, aplastic anemia, thrombocytopenia, leucopenia, hypoprothrombinaemia, and eosinophilia. Many of these effects on the blood may result from hypersensitivity reactions. Acute hemolytic anemia is a rare complication which may be associated with glucose-6-phosphate dehydrogenase deficiency."

"Other adverse effects which may be manifestations of a generalised hypersensitivity reaction to sulphonamides include a syndrome resembling serum sickness, liver necrosis hepatomegaly and jaundice, myocarditis, pulmonary eosinophilia and fibrosing alveolitis, and vasculitis including polyarteritis nodosa. Anaphylaxis has been reported only very rarely."

"Sulphonamides may rarely cause cyanosis due to methaemoglobinaemia."

"Other adverse reactions that have been reported after the administration of sulphamethoxazole or other sulphonamides include hypoglycaemia, hypothyroidism, neurological reactions including aseptic meningitis, ataxia, benign intercranial hypertension, convulsions, dizziness, drowsiness, fatigue, headache insomnia, mental depression, peripheral or optic neuropathies, psychoses, and vertigo, and pancreatitis."

"Slow acetylators of sulphamethoxazole may be at greater risk of adverse reactions than fast acetylators."

Other Information on Adverse Events.

Before presenting data on the dose given and the clinical signs and clinical pathology findings in adverse drug experience reports sent to the FDA over the past 25 or so years (primarily from pet owners and veterinarians) in dogs following oral administration of sulfadimethoxine, it is important to provide an overview of the FDA approved doses of sulfonamide drugs in dogs. The details of the FDA approved doses and uses of sulfonamide drugs can be found in Appendix C, which is an attached Microsoft Word document.

Overview of FDA Approved Total Daily Oral Doses of Sulfonamide Drugs in Dogs

Sulfachlorpyridazine -- 76.5 mg/kg bw to 110.2 mg/kg bw

Sulfadiazine (when combined with trimethoprim) -- 25.0 mg/kg bw per day (tablet)
22.05 mg/kg bw per day (oral suspension)
Do not treat (tablet and oral suspension) for more than 14 consecutive days

Sulfadimethoxine (when combined with ormetoprim) -- 45.8 mg/kg bw on 1st day and
22.9 mg/kg bw after 1st day but not to exceed a total of 21 consecutive days

Sulfadimethoxine (alone) -- 55.1 mg/kg bw on 1st day and
27.6 mg/kg bw after 1st day
For both tablets/boluses and oral suspension

Sulfamethizole (when combined with methenamine) -- 82.7 mg/kg bw per day

Sulfisoxazole -- 143.3 mg/kg bw per day

Comparison of Dose

I did not find any data in the published literature that provides good information on the lowest dose needed to produce the "hypersensitivity reaction" described above by 2 non-FDA sources in sulfonamide sensitive dogs or other animals, including man. Thus, I reviewed the approximately 1,225 adverse drug experience reports (ADER) associated with the oral administration of sulfonamides as drugs to dogs that FDA/CVM has received the past 25 years or so. Close attention was paid to the 53 ADER involving the sulfadimethoxine (SDMX) + ormetoprim combination and the 30 ADER with SDMX alone where the SDMX dose was characterized as less than the FDA approved oral dose. Following a careful review of the dose and the history and clinical signs in each

of these 83 reports (data available upon request), the dose in the vast majority of these ADER with a "less than FDA approved dose" were between 10 and 22 mg/kg bw per day and the lowest firmly established daily dose of SDMX in these reports where the clinical signs could not be readily explained by other causes was 8.8 mg/kg bw/day.

[Note: The ADER where the drug was administered at less than the FDA approved oral dose and the only effect reported was that the drug was ineffective against coccidia or bacteria were NOT included in the above assessment.]

[Note: Firmly established daily doses are reports where the number and strength of the tablets or the number of milliliters (ml) of the liquid (50 mg SDMX/ml) administered were provided as well as the current weight of the dog.]

COMPARISON OF CLINICAL SIGNS AND CLINICAL PATHOLOGY FINDINGS

FDA/CVM does not have any ADER associated with the oral administration of sulfaquinoxaline or sulfaclozine in dogs, but I believe they would likely be reasonably similar to those of other sulfonamide drugs. To assess how similar the clinical signs and clinical pathology findings associated with use of sulfadimethoxine (with and without ormetoprim) as a drug are to the clinical signs and clinical pathology findings reported in consumer complaints associated with the use of chicken jerky dog treats and with sweet potato dog treats manufactured in China, the following data was summarized and placed in Appendix D (see attached Excel document). I wish to thank Drs. Amy Neal, Renee Shibukawa-Kent and Lee Anne Palmer for their tremendous assistance in making Appendix D possible.

The first column represents all the clinical signs and clinical pathology findings from the 309 reports by FDA/CVM scientists over the past 25 years or so of ADER (primarily from pet owners and veterinarians) where the clinical signs and clinical pathology findings occurred within 48 hours (0-48 hours) of the first use of sulfadimethoxine (SDMX) with ormetoprim and were believed to be possibly to likely caused by the drug (causality assessment scores of 0 to 6).

The second column represents all the clinical signs and clinical pathology findings from the 272 reports by FDA/CVM scientists over the past ~ 25 years of all ADER (primarily from pet owners and veterinarians) where the clinical signs and clinical pathology findings were first noticed within 1-3 weeks (7-21 days) after the first use of sulfadimethoxine (SDMX) with ormetoprim. All ADER means the causality assessments scores ranged from minus 8 to 6 (-8 to 6) and included all clinical signs and clinical pathology findings except those related to the drug being ineffective against coccidia or as an antibiotic and those related to product defects (such as color of tablet).

Please note that the time to onset of clinical signs after first exposure to SDMX + ormetoprim can vary markedly from just a few minutes up to several weeks and that the following clinical signs were seen more often within the first 48 hours (0-2 days) than between 1 and 3 weeks (7-21 days):

Aggression	Apprehension/Agitated		Unspecified Behavior Changes	
Vocalization	Hallucination/Paranoia		Hypersalivation	
Ataxia	Trembling	Convulsions	Hyperactivity	Nervousness
Confusion	Hyperesthesia	Mydriasis	Polypnea	Tachycardia

The following clinical signs were seen more often between 1 and 3 weeks (7-21 days) than within 48 hours (0-2 days) after first exposure to SDMX + ormetoprim:

Evidence of liver damage/dysfunction – increased Alk Phos, ALT, AST and/or Total Bilirubin
Evidence of kidney damage/dysfunction—increased BUN and/or creatinine
Evidence of blood, bilirubin, protein and/or casts in urine

Anemia	Low platelet count	Ecchymoses/petechiae	
Pain/swelling of joints	Lameness	Stiffness	Weakness
Keratoconjunctivitis sicca	Conjunctivitis	Eye/lid problems	
Low thyroid hormone	Increased pancreatic enzymes	Bloody diarrhea/melena	
Anorexia	Weight loss	Icterus	Death

The third column represents all the clinical signs and clinical pathology findings from the 249 reviews by FDA/CVM scientists over the past 25 years or so of all ADER (primarily from pet owners and veterinarians) following the administration of SDMX alone (without ormetoprim). All ADER means the causality assessments scores ranged from minus 8 to 6 (-8 to 6) and included all clinical signs and clinical pathology findings except those related to the drug being ineffective against coccidia or as an antibiotic and those related to product defects (such as color of tablet).

The following clinical signs were reported slightly more often when using SDMX alone than when using SDMX + ormetoprim.

Vomiting	Diarrhea	Anaphylaxis/toid Reactions		
Pruritus	Urticaria	Alopecia	Skin Rash	Swelling and edema of head/face

From this review, it appears that adverse experiences reports with SDMX (with or without ormetoprim) can produce rather immediate effects (within 48 hours; 0 to 2 days) in some dogs and only after multiple daily exposures (1 to 3+ weeks; 7 to 21+ days) in others. It also appears that the following organs/systems can be affected -- liver, kidney, urinary, gastrointestinal, musculoskeletal, respiratory, neurologic, hematic, immune, dermal and pancreas.

The fourth column represents all the clinical signs and, due to time constraints, just some of the clinical pathology findings from 251 consumer complaints (primarily from dog owners and veterinarians) to FDA/CVM from 2006 to mid-2010 that were associated with the consumption of chicken jerky treats (almost all of which were believed to be manufactured in China). The chicken jerky treats mentioned in these 251 consumer complaints included Beefeaters, Bestros, Cadet, Canyon Creek, Carolina Prime, Dingo, Dogswell, Drs. Foster & Smith, Hartz, Kingdom Pets, Pet Center Inc., Pet Essentials, Pet Pride, Purina, Sergeant's, Smokehouse, Waggin' Train and Unknown/Other. The 4 most common brands mentioned first in the 251 complaints were Waggin' Train (102), Bestros (36), Kingdom Pets (35) and Smokehouse (16). All the other brands were mentioned first in 10 complaints or less.

The fifth column represents all the clinical signs and, due to time constraints, just some of the clinical pathology findings from 28 consumer complaints (primarily from dog owners and veterinarians) to FDA/CVM from about 2011 to May 2013 that were associated with the consumption of sweet potato dog treats that do not appear to contain any glycerin or any muscle or edible byproducts from poultry, beef or swine. Almost all of these sweet potato dog treats were believed to be manufactured in China.

The clinical signs and clinical pathology findings between the chicken jerky treats and the sweet potato treats were judged to be quite similar and together were judged to be reasonably close to those associated with SDMX + ormetoprim from 1-3 weeks (column 2), somewhat close to those associated with SDMX alone (column 3) and marginally close to those associated with SDMX + ormetoprim from 0-48 hours (column 1). One clinical pathology finding was reported only in the chicken jerky and the sweet potato dog treats (and was not reported in any of the SDMX ADER in dogs) and this finding was a Fanconi-like syndrome (FLS). For this report, a FLS is defined as elevated levels of amino acids in the urine and/or as elevated glucose levels in the urine with low or normal levels of glucose in the blood.

The following clinical signs and clinical pathology findings were reported more often (~2+ times higher on a percentage basis) in the consumer complaints from the chicken jerky and sweet potato dog treats (columns 4 and/or 5) than from the ADER with SDMX (with or without ormetoprim) (columns 1 and/or 2 and/or 3).

Dehydration	Vomiting	Bloody vomiting	Diarrhea	Bloody Diarrhea
Polyuria	Polydipsia	Adipsia	Urinary Incontinence	Kidney failure/damage/dysfunct

The following clinical signs were reported slightly more often (~1.5 times higher on a percentage basis) in the consumer complaints from the chicken jerky and sweet potato dog treats (columns 4 and/or 5) than from the ADER with SDMX (with or without ormetoprim) (columns 1 and/or 2 and/or 3).

Depression/lethargy	Anorexia	Weight Loss
Protein in the urine	Low urine specific gravity	Death (includes euthanized)

Finally, it is worth noting that although the gastrointestinal and kidney related clinical signs and clinical pathology findings were the predominant ones reported with the chicken jerky treats and the sweet potato treats, the chicken jerky and/or sweet potato treats were also associated with a few reports where the primary effect was

liver (elevated liver enzymes and/or icterus),
respiratory (panting and/or tachypnea and/or dyspnea and/or coughing),
hematic (low blood platelets and/or anemia),
neurologic (convulsions, confusion, behavior disorder not otherwise specified, vocalization),
musculoskeletal (ataxia, trembling, weakness, recumbency, reluctant to move),
dermal (pruritus, urticaria, welts, rash and/or alopecia),
and/or pancreas (elevated lipase and amylase)

in nature. In addition, keratoconjunctivitis sicca was reported in one consumer complaint for both the chicken jerky and the sweet potato dog treats.

Thus, overall, I would assess the clinical signs/clinical pathology findings (with the exception of Fanconi-like syndrome) associated with ADER with SDMX (with and without ormetoprim) to be somewhat to reasonably close to those reported in the chicken jerky and sweet potato dog treats. In addition, since FDA/CVM has received many reports of adverse effects within 48 hours (2 days) of first exposure and also many reports of adverse effects within 1 to 3 weeks (7 to 21 days) or even longer following the first exposure to the chicken jerky and sweet potato dog treats (personal

assessment following review of the consumer complaints), I would assess the time course associated with adverse effects to be reasonably close to those reported with SDMX (with or without ormetoprim).

The major problems that I perceive in concluding that the adverse effects reported in the consumer complaints associated with Milo's Kitchen chicken jerky dog treats are caused by ppb levels (not corrected for recovery) of sulfaquinoxaline, sulfaclozine and sulfamethoxazole are the following:

1) The highest daily dose provided by the combined residues of 3 sulfonamide drugs found on the chicken jerky dog treats even when the residues found are corrected for recovery and assumed to comprise 100% of the diet of a very small breed adult dog (calculations for a practical worst case scenario to follow in sections below) is 0.15 mg/kg bw and this dose is 147 times lower than the lowest FDA approved daily therapeutic dose for a sulfonamide drug in dogs (22.05 mg/kg bw). [22.05 / 0.15 = 147].

2) The lack of solid data in the published literature[1] on the lowest oral or dietary dose of sulfonamide drugs or sulfonamide pesticides shown to produce the clinical signs/clinical pathology findings described above in "hypersensitive" dogs or other animals, including man.

3) I am not aware of any testing for sulfonamide drugs or sulfonamide pesticides that have been conducted on the sweet potato only dog treats that appear to be manufactured in China and produce clinical signs and clinical pathology findings quite similar to those reported in association with chicken jerky dog treats (compare columns 4 and 5 of Appendix D). If similar levels of the same sulfonamide drugs as those reported by SNYDAM FL in chicken jerky treats are found on the sweet potato dog treats or if levels of sulfonamide pesticides are found at levels above an EPA tolerance on the sweet potato dog treats, this would strengthen the possibility that parts per billion (ppb) residues of sulfonamides (drugs and/or pesticides) are capable of producing a "hypersensitivity" reaction in dogs at low levels. If no such levels are found on the sweet potato dog treats, then the likelihood that ppb sulfonamide levels are the cause of the adverse reactions in dogs will decrease due to the close similarity of clinical signs and clinical pathology findings in consumer complaints for the chicken jerky and sweet potato dog treats manufactured in China.

4) Since almost 89% (56/63 = 0.889 = 88.9%) of the Milo's Kitchen chicken jerky subsamples tested by SNYDAM FL contained LESS THAN 85 ppb of total sulfonamides (sulfaquinoxaline plus sulfaclozine plus sulfamethoxazole) on a recovery corrected basis, I believe there is a distinct possibility that the vast majority of the sulfonamide drug residues found are simply incidental findings and are not the cause of the reported adverse effects.

In any event, when dealing with the scientific uncertainty, especially regarding dose, which abounds with potential hypersensitivity reactions, I believe it is best to find solid scientific ground and use safety factors and practical worst case scenarios to determine the cutoff points for a Class I, II and

[1] Searches were performed of the published literature using the tools in the FDA library to find relevant scientific information on sulfonamide drugs or pesticides and hypersensitivity in man and other animals and there was a lack of solid data in regards to dose.

III recall. In this situation, I believe the following two 90-day oral toxicity studies with sulfaquinoxaline in beagle dogs, which can be found in [Veterinary] Master File (b) (4), provide the solid scientific ground upon which to determine these cutoff points.

I will summarize these two 90-day studies first and then describe the safety factors and the practical worst case scenarios that I used to determine the cutoff levels for a class I, a class II and a class III recall for chicken jerky treats found to contain sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole). I will then indicate which of the 5 lots of Milo's Kitchen Chicken Jerky dog treats analyzed by SNYDAM FL should be considered a candidate for recall and at what level of recall for these 3 sulfonamide drugs (when found both singly and in combination) and for the other 3 drugs that were analyzed (tilmicosin, enrofloxacin and trimethoprim).

Ninety Day Oral Toxicity Study with Sulfaquinoxaline in Dogs – I

Twenty male (weighing from 7.5 to 10.0 kilograms) and 20 female (weighing from 5.4 to 9.6 kilograms) beagles were used in this study. Four male and 4 female dogs were used at each dosage level (2, 6 and 18 mg of sulfaquinoxaline) and also in 2 control groups.

The compound (sulfaquinoxaline) was an off-yellow colored powder and was identified as "Sulfaquinoxaline, N.S. for MFG., 2-89662, Lot – V 2-51-0, Assay – 99.9%, 8069-275 300 grams". The compound was administered in gelatin capsules 7 days each week. The control dogs received empty gelatin capsules on the same regimen as treated dogs. Individual daily doses were based upon the body weights obtained weekly.

The dogs were observed daily for changes in general behavior and appearance. Individual body weights and food consumption were recorded weekly. Once in the control period and at 1, 2 and 3 months of study, physical and ophthalmoscopic examinations were performed on all of the dogs.

Once in the control period and at 1, 2 and 3 months of study, T3 (triiodothyronine) and T4 (thyroxine) determinations were conducted for all of the dogs. Twice in the control period and at 0.5, 1, 2 and 3 months of study, blood and urine samples were obtained from all dogs for the following analyses.

Hematology: Hematological studies included hemoglobin, hematocrit, erythrocyte sedimentation rate, total and differential leukocyte counts, coagulation time and prothrombin time.

Biochemistry: Biochemical studies included fasting plasma glucose, plasma urea nitrogen, creatinine, total protein, albumin, protein electrophoresis, alkaline phosphatase activity, serum glutamic oxalacetic transaminase activity, and T3 and T4.

Urinalysis: Urinalysis included qualitative tests for albumin, bilirubin, glucose and occult blood and microscopic examination of the sediment.

Gross Pathology, Organ Weights and Histopathology: Following 90 days of study, all of the dogs were sacrificed and necropsied. The following organs were weighed – **adrenals, brain, heart, kidneys, liver, pituitary, spleen, testes/ovaries, and thyroid with parathyroid**.

The following tissues from each dog were collected in buffered neutral 10% formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically – **adrenals, bone marrow, brain, eye, gall bladder, heart, kidneys, large intestine, liver, lung, lymph node, pancreas, pituitary, prostate/uterus, salivary gland, sciatic nerve, skeletal muscle, skin, small intestine, spleen, stomach, testes/ovaries, thymus, thyroid/parathyroid, and urinary bladder.**

Oil red 0 stained frozen sections of **liver** and **kidney** and a Wright-Giemsa stained **bone marrow** smear from each dog also were prepared and examined. Aldehyde fuchsin stained sections of pituitary from representative dogs from the control, 6 and 18 mg/kg/day dosage level groups also were prepared and examined.

Results. No changes in general behavior or appearance considered to be related to compound were seen. No dogs died during the study. No changes considered to be related to compound were seen during ophthalmoscopic and physical examinations.

Increases in body weight were similar for control and treated dogs. Food consumption values were similar for control and treated dogs, all of whom were fed 300 grams of Purina Dog Chow once per day and had ad libitum availability to water.

There were differences noted in the High Dosage Group (18 mg/kg bw/day).

Coagulation times for dogs in the high dosage group generally were higher than those of control or other treated dogs at all intervals of analysis. At 0.5 months of study, elevated prothrombin times were noted for all dogs in the high dosage group. Serum creatinine levels were increased for 2 or more dogs in the high dosage group at 1 and 2 months of treatment. Two female dogs in the high dosage group had elevated erythrocyte sedimentation rates (ranging from 8 to 18 mm/hr) at the 2 and 3 month intervals of analysis. At 3 months of study, hemoglobin and hematocrit values for dogs in the high dosage group were generally lower than those of control dogs.

Markedly enlarged **thyroid** glands were noted at gross necropsy in all dogs from the high dosage group and one male dog had a congested thyroid.

The absolute and relative **thyroid with parathyroid** weights of dogs in the high dosage group were statistically higher than control values in both sexes. The absolute and relative **pituitary** weights of just the males in the high dosage group were statistically higher than the control values.

Most dogs in the high dosage group had moderate to severe **thyroid** hyperplasia, characterized by diminution or absence of colloid, increased size and number of follicular epithelial cells with infolding or epithelial cells into the follicles and increased mitotic activity.

Three dogs in the high dosage group (2 males and 1 female) had many degranulated and/or vacuolated glandular epithelial cells in the anterior lobe of the **pituitary**.

Seven dogs in the high dosage group had moderate to marked **thymic** involution.

All male dogs from the high dosage group were aspermic. In **testes** from these dogs, spermatogonia, primary and secondary spermatocytes were present, but spermatids were essentially absent and no spermatozoa were present.

An inspissated, mucus-like granular bile was found at gross necropsy in the **gall bladder** of 5 dogs (3 females and 2 males) from the high dosage group. Three dogs (2 male and 1 female) in the high dosage group had very slight amounts of finely divided lipid in **hepatocyte** cytoplasm. Lipid was limited to midzonal and peripheral cells in the individual **liver** lobules and many lobules were unaffected.

Adrenal glands from 3 female dogs in the high dosage groups had slight to moderate vacuolation of groups of cortical cells of the zona fasciculata. Two of these 3 female dogs had luteal cysts in their **ovaries** and 1 of these 2 dogs also had moderate periarteritis in its ovaries.

Differences were also noted in the Middle Dosage Group (6 mg/kg bw/day).

Markedly enlarged **thyroid** glands were noted at gross necropsy in all dogs from the middle dosage group. The absolute and relative **thyroid with parathyroid** weights of dogs in the middle dosage group were statistically higher than control values in both sexes.

Most dogs in the middle dosage group had moderate to severe **thyroid** hyperplasia, characterized by diminution or absence of colloid, increased size and number of follicular epithelial cells with infolding or epithelial cells into the follicles and increased mitotic activity.

Testes of 2 of the 4 male dogs from the middle dosage group were considered oligospermic. In these testes, mature spermatozoa were present, but in reduced numbers, spermatids were undergoing degeneration and occasional syncytial giant cells were found in seminiferous tubules.

An inspissated, mucus-like granular bile was found at gross necropsy in the **gall bladder** of 2 females from the middle dosage group. Three dogs (2 male and 1 female) in the middle dosage group had very slight or moderate or marked amounts of finely divided lipid in **hepatocyte** cytoplasm. In all but the most markedly affected dog (a male), lipid was limited to midzonal and peripheral cells in the individual **liver** lobules and many lobules were unaffected.

Differences in the Low Dosage Group (2 mg/kg bw/day) were also found.

The absolute thyroid with parathyroid weight of both males and females and the relative thyroid with parathyroid weight of the females were statistically higher then control values.

Ninety Day Oral Toxicity Study with Sulfaquinoxaline in Dogs – II

Since the lowest dosage tested (2 mg/kg bw/day) in the first 90-day oral toxicity study with sulfaquinoxaline in dogs had adverse effects, a second study was conducted at lower dosages to try and establish a no-observed-effect level (NOEL).

Twenty-four male (weighing from 7.0 to 10.6 kilograms) and 24 female (weighing from 6.4 to 10.1 kilograms) beagles were used in this study. Four male and 4 female dogs were used at each dosage level (0.5, 1.0, 1.5 and 2.0 mg of sulfaquinoxaline) and also in 2 control groups.

The compound (sulfaquinoxaline) was an off-yellow colored powder and was identified as "Sulfaquinoxaline, 2-89662 9027-40, Lot V 2-51-0 150 grams". The compound was administered in gelatin capsules 7 days each week. The control dogs received empty gelatin capsules on the same regimen as treated dogs. Individual daily doses were based upon the body weights obtained weekly.

Water was available ad libitum and 300 grams of Purina Dog Chow was fed to each dog once a day. The iodine content of the Purina Dog Chow was determined on 4 different bags of food (a single lot of food was used for the study) and the average iodine content was 5.4 ppm.

The dogs were observed daily for changes in general behavior and appearance. Individual body weights and food consumption were recorded weekly. Once in the control period and at 1, 2 and 3 months of study, physical and ophthalmoscopic examinations were performed on all of the dogs.

Once in the control period and at 5, 9 and 13 weeks of study, T3 and T4 determinations were conducted for all of the dogs. Twice in the control period and at 0.5, 1, 2 and 3 months of study, blood and urine samples were obtained from all dogs for the following analyses.

Hematology: Hematological studies included hemoglobin, hematocrit, erythrocyte sedimentation rate, total and differential leukocyte counts, coagulation time and prothrombin time.

Biochemistry: Biochemical studies included fasting plasma glucose, plasma urea nitrogen, creatinine, total protein, albumin, protein electrophoresis, alkaline phosphatase activity, serum glutamic oxalacetic transaminase activity, and T3 and T4.

Urinalysis: Urinalysis included qualitative tests for albumin, bilirubin, glucose and occult blood and microscopic examination of the sediment.

Gross Pathology, Organ Weights and Histopathology: Following 90 days of study, all of the dogs were sacrificed and necropsied. The following organs were weighed – **adrenals, brain, heart, kidneys, liver, pituitary, spleen, testes/ovaries, and thyroid with parathyroid**.

The following tissues from each dog were collected in buffered neutral 10% formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically – **adrenals, liver, pituitary, testes/ovaries, thymus, and thyroid/parathyroid**. Microscopic examination was done in a "blind" manner with treatment group identity unknown to the pathologist at the time of examination.

Results. No changes in general behavior or appearance considered to be related to the compound were seen. No dogs died during the study. No changes considered to be related to the compound were seen during the ophthalmoscopic and physical examinations.

Increases in body weight were similar for control and treated dogs. Food consumption values were similar for control and treated dogs.

No changes considered to be related to the compound were seen in hematological studies. Incidental findings included a low normal hemoglobin and hematocrit at 2 months and a slight elevation in erythrocyte sedimentation rate at 3 months for 1 dog at the 1.0 mg/kg/day dosage level. A slight increase in total leukocytes also was noted for 1 dog at the 2.0 mg/kg/day dosage level at 2 months of study.

No changes considered to be related to compound were seen in biochemical studies and this includes T3 and T4 values.

No changes or unusual values were seen in urinalysis values.

No compound related gross pathological or histopathological lesions were observed at necropsy or in any tissues examined from any dogs in the experimental groups.

Differences were noted in the 1.5 and 2.0 mg/kg bw/day groups.

At 1.5 and 2.0 mg/kg/day, the group mean (male plus female) relative thyroid weights were statistically increased ($P<0.01$) compared to the combined control group (male plus female from control group 1 and control group 2).

There were no statistical differences between the group mean (male plus female) relative thyroid weights of the 1.0 and 0.5 mg/kg/day groups compared to the combined control group.

However, following review of these data by a Bureau of Veterinary Medicine scientist the following observations were made:

"The 1.0 mg/kg level [for relative thyroid weight] was not significant ($p>0.30$) from the control. Since there were only 16 dogs in the control group and 8 dogs in the 1.0 mg/kg group the power to detect an increase of 11% in the relative thyroid weights if one exists is only around 17%. Thus, there is a very low probability of finding a significant difference with an 11% increase over control. Stated another way, the probability of accepting the hypothesis that the two group means are equal when they differ by as much as 11% is around 83%. In fact to reach a power of 50% for the size samples mentioned above, there would have to be an increase of about 23% over the control value.

A regression analysis showed a significant ($p<0.001$) linear increase in the relative thyroid weights as the level of dose increased. Also the 95% confidence limits on the expected value under a linear model at the 1.0 mg/kg level do not overlap the control confidence limits. Thus, there is a significant ($p<0.05$) difference between the predicted control mean and the predicted 1.0 mg/kg level mean. In the regression analysis performed there was no significant ($p>0.05$) departure from linearity…

In summary, no statistical difference was found between the observed relative thyroid weights at the 1.0 mg/kg level and the control. But due to the low number of animals used, the low power to detect a difference if one exists, and the significant positive linear regression found there remains a doubt as to whether or not the 1.0 mg/kg level can be called a no-effect level."

This above statistical review of the data lead to the following comments from the Chief of the Therapeutic Products Branch, Division of Drugs for Swine and Minor Species, Bureau of Veterinary Medicine in a letter dated June 29, 1979.

1. Our reevaluation of the available dog feeding study obtained with sulfaquinoxaline indicates that the highest observed "no-effect" level is 0.5 mg/kg.

2. The negligible tolerance is 25 ppb based upon this highest observed "no-effect" level.

In a memorandum dated September 28, 1981, the Chief of the Food Animal Additive Evaluation Branch makes the following statements to a scientist on the Food Animal Additives Staff:

1. We are in concurrence with your option #2 in which the continued interim listing of sulfa Q will be allowed pending an agreement with the sponsor to conduct new studies. We agree that with the present data available to the agency a tolerance of 0.1 ppm can not be met.

2. Based upon the results of the firm's 90 day dog study a negligible tolerance of 0.025 ppm can be applied. However, the firm's tissue residue assay method supposedly is not sensitive enough to detect these residue levels…

DISCUSSION

Please note that sulfaquinoxaline, which is not approved by the FDA as a drug in dogs, appears to be much more toxic to dogs than all 5 sulfonamide drugs approved by the FDA in dogs (sulfachlorpyridazine; sulfadiazine when combined with trimethoprim; sulfadimethoxine by itself and when combined with ormetoprim; sulfamethizole when combined with methenamine; and sulfisoxazole). This is because when sulfaquinoxaline was administered daily in a gelatin capsule for 90 days at 18 mg/kg bw it produced many different serious adverse health effects in all dogs in the high dose group. This dose (18 mg/kg bw /day) is slightly to significantly lower than the FDA approved daily doses (22.05 to 143.3 mg/kg/day) for the 5 sulfonamide drugs approved by the FDA for use in dogs (albeit some of these 5 FDA approved drugs in dogs may only be permitted for 14 or 21 consecutive days of use).

For this Health Hazard Evaluation (HHE), the above mentioned "negligible tolerance of 0.025 ppm [25 ppb]" for sulfaquinoxaline mentioned in [Veterinary] Master File (b) (4) will NOT apply as there is a 0.1 ppm [100 ppb] tolerance currently listed for sulfaquinoxaline in uncooked edible byproducts of chickens in 40 CFR 556.685. If the CVM Office of New Animal Drug Evaluation (ONADE) believes this 0.1 ppm tolerance for sulfaquinoxaline should be lowered, then CVM/ONADE would likely need to publish a document in the Federal Register and receive and respond to public comments before any change could be initiated in 21 CFR 556.685. While I will use the current 0.1 ppm tolerance to establish where a class III recall will begin with sulfaquinoxaline, I will use what I consider the best available science (NOEL of 0.5 mg/kg bw/day from the second 90-day oral toxicity studies in dogs in [Veterinary] Master File (b) (4)) to help establish where a class II recall will begin.

To convert this 100 ppb tolerance level in uncooked edible tissues (estimated to contain 75% moisture and 25% dry matter) to an equivalent level in chicken jerky (15% moisture and 85% dry matter), I used the following equation:

100 ppb x (85% dry matter/25% dry matter) = 100 ppb x 3.4 = 340 ppb

Thus, any chicken jerky (15% moisture) containing more than 340 ppb of sulfaquinoxaline would exceed the current human tolerance on this commodity and could be considered violative by the FDA in dry pet treats (15% moisture). It is important to note that the tolerances established for sulfaquinoxaline and other sulfonamide drugs in 21 CFR 556 are for human food; however, if these human food tolerances are exceeded in pet food then CVM could consider taking regulatory action (e.g., class III recall, etc.). Sulfaclozine has a zero tolerance established in 21 CFR 556.625 for residues (of sodium sulfachloropyrazine monohydrate) in uncooked edible tissues of chickens and no tolerances have been established for sulfamethoxazole in 21 CFR 556. Thus, for both of these sulfonamide drugs (sulfaclozine and sulfamethoxazole) any quantifiable level in chicken jerky pet treats above these tolerances could be considered violative and CVM could consider taking regulatory action.

On some of the chicken jerky strips tested, the SNYDAMFL found quantifiable residues of two or more sulfonamide drugs. Since I believe the toxicity of the sulfonamide drugs is additive, I believe CVM should use total sulfonamide residues in determining what action, if any, to take. Since SNYDAMFL reported fairly low recoveries for sulfamethoxazole, sulfaclozine and sulfaquinoxaline, I also believe the analytical findings should be corrected for recovery before determining if the sulfonamide level, whether it is from one or more sulfonamide drugs, would be

considered violative. When there are multiple sulfonamide drugs present at quantifiable levels, I believe the safety assessment should assume that the entire combined sulfonamide level came from the drug that is most toxic to the species of interest. Sulfaquinoxaline appears to be the most toxic sulfonamide drug tested in dogs to date and I could not locate any oral or dietary toxicity studies with sulfaclozine or sulfamethoxazole in dogs.

The above said correction for recovery was deemed necessary because the recoveries reported by the SNYDAM FL were fairly low. In samples spiked at 30 ppb, which was the highest level added to samples tested for recovery by SNYDAMFL, the average recovery for sulfaclozine and sulfaquinoxaline was 59.5% and 33.0%, respectively. The recovery corrected levels for sulfaclozine and sulfaquinoxaline can also be found in Appendix A (pages 6 - 10).

For instance, if a lab found 80 ppb of sulfaclozine in the chicken jerky and the percent recovery of the lab for sulfaclozine spiked at 50 ppb was 60% and the lab also found 70 ppb of sulfaquinoxaline and the percent recovery of the lab for sulfaquinoxaline spiked at 50 ppb was 33%, then this would equate to a combined total of 345 ppb of sulfaquinoxaline and sulfaclozine in the chicken jerky. Since this combined recovery corrected level for these 2 sulfonamide drugs is greater than the above mentioned 340 ppb level for sulfaquinoxaline on chicken jerky, then I believe this theoretical sample could be considered violative by the FDA when this treat is likely to be fed to dogs.

60% = 0.6
80 ppb / 0.6 = 133 ppb

33% = 0.33
70 ppb / 0.33 = 212 ppb

133 ppb + 212 ppb = 345 ppb

Thus, a class III recall would be any lot of chicken jerky where the combined recovery corrected levels for quantifiable residues of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) in one or more dog treat(s) exceed 340 ppb (0.340 ppm) but are less than or equal to 1.25 ppm (1,250 ppb) (see class II recall discussion below for how the 1,250 ppb level was derived). A class III recall is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

A class II recall would be any lot of chicken jerky where the combined recovery corrected levels for sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) in one or more dog treat(s) exceed the lifetime NOEL for sulfaquinoxaline in dogs on a practical worst case scenario basis.

As mentioned above the 90 day no-observed-effect level (NOEL) for sulfaquinoxaline in dogs following oral capsule administration was established at 0.5 mg/kg bw/day. To convert a 90-day NOEL to a lifetime NOEL, I will divide the 90-day NOEL by a safety factor of 10. Thus, the lifetime NOEL for sulfaquinoxaline in dogs is 0.05 mg/kg bw/day [0.5 mg/kg bw/day divided by 10 = 0.05 mg/kg bw/day].

A practical worst case scenario will be defined as the chicken jerky comprising 100% of the total diet of a very small breed adult dog on a daily basis. The beagle dogs in the sulfaquinoxaline studies weighed approximately 10 kg and gained weight when fed 300 g of dry dog food per day. This equates to adult beagles consuming approximately 3% of their body weight in dry food per day. 300 g = 0.3 kg; 0.3 kg divided by 10 kg = 0.03 = 3%

For this calculation, I will assume that very small breed adult dogs consume 4.0% of their body weight in dry dog food per day.

A 5 kg dog that consumes 4.0% of its body weight in chicken jerky per day would consume 200 grams of chicken jerky [5 kg bw x 0.040 kg of food/kg bw = 0.200 kg of food = 200 g].

5 kg bw x 0.05 mg of sulfaquinoxaline / kg bw [lifetime NOEL] = 0.25 mg of sulfaquinoxaline

0.25 mg of sulfaquinoxaline / 0.200 kg of chicken jerky = 1.25 mg of sulfaquinoxaline/kg of chicken jerky = 1.25 ppm of sulfaquinoxaline = 1,250 ppb of sulfaquinoxaline

Thus, any lot of chicken jerky that contains one or more dog treat(s) with more than 1.25 ppm (1,250 ppb) and less than or equal to 15.0 ppm (15,000 ppb) (see class I recall discussion below for how the 15,000 ppb level was derived) of sulfaclozine plus sulfaquinoxaline (plus sulfamethoxazole) on a recovery corrected basis would be considered a class II recall. This is because exposure to this product may cause temporary or medically reversible health consequences or where the probability of serious adverse health consequences is remote.

It is worth noting, that the two dog treats with the highest combined level of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) on a recovery corrected basis averaged 3.74 mg/kg (ppm) [(3.77 + 3.71 ppm)/2 = 3.74], but were only found in 2 of 63 subsamples tested. If one assumes that all treats in a bag contained similar levels of these sulfonamide drugs and were consumed at 4.0% of their body weight per day, then the daily sulfonamide drug dose from these treats would be about 0.15 mg/kg bw (see calculation below) which is about 3.0x the daily lifetime NOEL for sulfaquinoxaline in dogs of 0.05 mg/kg bw [0.15 / 0.05 = 3.0].

3.74 mg of sulfaquinoxaline + sulfaclozine / kg of dog treat x 0.040 kg of dog treat / kg bw = 0.1496 (which I will round up to 0.15) mg of sulfaquinoxaline plus sulfaclozine / kg bw)

A class I recall will be defined as any lot of chicken jerky that contains one or more dog treat(s) where the combined recovery corrected levels of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) would provide a dose of above 0.6 mg/kg bw/day on a practical worst case scenario basis. The 0.6 mg/kg bw/day dosage was derived by taking the daily dosage given to the middle group (6 mg/kg bw) in the first 90 day oral toxicity study with sulfaquinoxaline in dogs and dividing it by a factor of 10. This lifetime daily dose of 0.6 mg/kg bw would be expected to produce the following serious adverse health consequences – markedly enlarged thyroid glands; moderate to severe thyroid hyperplasia; oligospermia; excessive lipid accumulation in the liver. Thus, on a lifetime daily exposure basis at 0.6 mg/kg bw, there is a reasonable probability that a serious adverse health consequence or death would occur. On a practical worst case basis, this equates to 15.0 ppm (15,000 ppb) of sulfaquinoxaline in the chicken jerky (see calculations below).

5 kg bw x 0.6 mg of sulfaquinoxaline / kg bw = 3.0 mg of sulfaquinoxaline

3.0 mg of sulfaquinoxaline / 0.200 kg of chicken jerky = 15.0 mg of sulfaquinoxaline/kg of chicken jerky = 15.0 ppm of sulfaquinoxaline = 15,000 ppb of sulfaquinoxaline.

Using the above said rationale, there are three lots (1320 HVC and 1325 HVC and 1272HVA) of Milo's Kitchen chicken jerky that contained no dog treats where the combined recovery corrected levels of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) exceeded

the 340 ppb level described above and these lots would not need to be recalled based on the SNYDAM FL analyses for combined sulfonamide drug residues containing in part quantifiable residues of sulfaquinoxaline.

There was one lot (1304 HVC) of Milo's Kitchen chicken jerky where one or more dog treats had a combined recovery corrected level of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) above 340 ppb and less than or equal to 1.25 ppm (1,250 ppb) and this lot would be considered a class III recall based on the SNYDAM FL analyses.

There was one lot (2243 HVB) of Milo's Kitchen chicken jerky where one or more dog treats had a combined recovery corrected level of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) above 1.25 ppm (1,250 ppb) and less than or equal to 15.0 ppm (15,000 ppb) and this lot would be considered a class II recall based on the SNYDAM FL analyses.

There were no lots of Milo's Kitchen chicken jerky where one or more dog treats exceeded the combined recovery corrected level for sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) of 15.0 ppm (15,000 ppb). Thus, there were no lots of Milo's Kitchen chicken jerky that would be considered a class I recall based on the SNYDAM FL analyses.

It is important to recognize that the 5 samples analyzed by the SNYDAM FL were collected off the shelf at retail and were not known to be associated with any consumer complaints to FDA/CVM or SNYDAM at the time of collection. FDA did receive FACTS consumer complaint #130206 on January 16, 2013 where a 14-year-old male neutered cockapoo developed diarrhea, excessive thirst, frequent urination, and urinary incontinence after consuming 4 Milo's Kitchen chicken jerky (MKCJ) treats per day for about 6 months. MKCJ lot number 2243HVB came from a 23 [likely meant 20 or 3.3] oz plastic bag that was purchased in December 2012 and appeared to be the lot fed immediately prior to and during the time the clinical signs were noted. On January 16, 2013, the complainant indicated the dog had shown the clinical signs noted above for weeks and that the dog was taken to a veterinary clinic about 1 month ago and blood tests showed loss of kidney function.

Thus, only one of the five lots of Milo's Kitchen Chicken Jerky (MKCJ) that were analyzed by SNYDAM FL has also been listed in a consumer complaint sent to the FDA and this lot was 2243HVB. It is worth noting that the two subsamples of MKCJ (out of the 63 tested by SNYDAM FL) that contained by far the highest levels of both sulfaclozine and sulfaquinoxaline also came from lot 2243HVB; however, lot number data are often not provided in the consumer complaints sent to FDA; some consumer complaints list several lot numbers from the same and/or different brands of chicken jerky; and sulfaclozine and sulfaquinoxaline levels varied greatly both within and between the 5 lots tested.

The Animal Health Hazard Evaluation Committee has also asked me to discuss the potential for recalls and the class of the potential recall in the 5 lots of MKCJ tested based solely on the levels of non-sulfonamide drugs and also in subsamples containing sulfaclozine and/or sulfamethoxazole (excluding the sulfaquinoxaline data).

In 4 of the 5 lots of MKCJ that were tested (Lots 1320HVC and 1325HVC and 2243HVB and 1272 HVA), 1 of 10 subsamples contained a quantifiable level of tilmicosin (6.75 ppb, 6.37 ppb, 6.40 ppb and 25 ppb, respectively). Since there are no tolerances established by the FDA for tilmicosin in chicken products or byproducts in 21 CFR 556.735, these quantifiable residues of tilmicosin in chicken jerky could be considered a violation of the Federal Food, Drug and Cosmetic Act as amended (the Act) and potentially lead to a class III recall.

In MKCJ from Lot 1272 HVA, 1 of 10 subsamples contained a quantifiable level of enrofloxacin (14 ppb). Since there are no tolerances established by the FDA for enrofloxacin in chicken products or byproducts in 21 CFR 556.226, this quantifiable residue of enrofloxacin in chicken jerky could be considered a violation of the Act and potentially lead to a class III recall.

In MKCJ from Lot 1325HVC, 6 of 10 subsamples contained quantifiable levels of sulfaclozine that ranged from 4.28 to 10.6 ppb. Although there is a zero tolerance established for sulfaclozine in the uncooked edible tissues of chickens in 21 CFR 556.625, only ONE of these 6 subsamples (the one containing 10.6 ppb) could be considered a violation of the Act and potentially lead to a class III recall.

This assumes that the limit of detection (3.0 ppb) in the analytical method used for the chicken jerky is the same as that for the uncooked edible tissues of chickens. If this is the case, then the chicken jerky would need to contain at least 10.2 ppb of sulfaclozine to exceed the assumed 3.0 ppb limit of detection in the uncooked edible tissues of chickens. This is shown in the equation below and accounts for differences in percent dry matter between the chicken jerky and the uncooked edible tissues of chickens.

10.2 ppb x (25% dry matter divided by 85% dry matter) =
10.2 ppb x (1 divided by 3.4) =
10.2 ppb x 0.294 = 3.0 ppb

In MKCJ from Lot 2243HVB, 9 of 10 subsamples contained quantifiable levels of sulfaclozine that ranged from 3.47 to 751 ppb. Although there is a zero tolerance established for sulfaclozine in the uncooked edible tissues of chickens in 21 CFR 556.625, only SEVEN of these 9 subsamples (the ones containing ≥10.2 ppb) could be considered a violation of the Act (based on the assumptions above) and potentially lead to a class III recall.

In MKCJ from Lot 1272HVA, 9 of 10 subsamples contained quantifiable levels of sulfaclozine that ranged from 3.8 to 100 ppb. Although there is a zero tolerance established for sulfaclozine in the uncooked edible tissues of chickens in 21 CFR 556.625, only FIVE of these 9 subsamples (the ones containing ≥10.2 ppb) could be considered a violation of the Act (based on the assumptions above) and potentially lead to a class III recall.

In MKCJ from Lot 1304HVC, 16 of 23 subsamples contained quantifiable levels of sulfaclozine that ranged from 3.4 to 367 ppb. Although there is a zero tolerance established for sulfaclozine in the uncooked edible tissues of chickens in 21 CFR 556.625, only SEVEN of these 16 subsamples (the ones containing ≥10.2 ppb) could be considered a violation of the Act (based on the assumptions above) and potentially lead to a class III recall.

No quantifiable residues of sulfamethoxazole or trimethoprim were detected in any of the 63 subsamples tested. Thus, there were no violations of the Act from residues of these 2 drugs in the 5 lots of MKCJ that were tested. Since no tolerances have been established for either of these two drugs in 21 CFR 556, any quantifiable residue of sulfamethoxazole or trimethoprim could be considered a violation of the Act and potentially lead to at least a class III recall depending on the levels found.

Thus, overall, all 5 lots of Milo's Kitchen chicken jerky that were analyzed contained a drug residue(s) that could be considered a violation of the Act. In 4 of the 5 lots (1320 HVC and 1325 HVC and 1272HVA and 1304HVC) the violation could potentially lead to a class III recall, while in lot 2243HVB the violation could potentially lead to a class II recall.

Review:

Sample collection:
Aseptic technique [ ] Yes [X] No [ ] NA
Number of subsamples: 63

Was chain of custody documented correctly?
[X] Yes
[ ] No Explain in narrative box:
[ ] NA Samples collected by recalling firm.

Analytical method: [X] Yes [ ] No [ ] NA
[ ] Official method
[ ] FDA LIB method
[X] Other methods, explain in narrative box: LC-MS/MS

Was analysis properly conducted?
[X] Yes
[ ] No Explain in narrative box:
[ ] Unknown

Laboratory analysis: [X] Yes [ ] No [ ] NA
Done by: [ ] FDA Laboratory
[X] State laboratories – State of New York State Department of Agriculture and Markets Food Laboratory
[ ] Other
[ ] None

Have any adverse reaction reports or other indication of injuries or diseases been reported relating to this problem?
[ ] No
[X] Yes Attach copies or explain in narrative box: FACTS consumer complaint #130206 will be attached to this HHE when the appropriate data in this complaint have been redacted because of privacy issues.
[ ] NA

Is the problem easily identified by the user?
[X] No
[ ] Yes

What are the animal and human populations at risk?

The animal population at greatest risk would be dogs with a sulfonamide sensitivity that consumed a recalled lot of dog treats containing more than 1,250 ppb (1.25 ppm) of total sulfonamides (sulfaquinoxaline + sulfaclozine + sulfamethoxazole) as a major portion of their complete diet.

Sulfonamide sensitive humans that consume these dog treats could also potentially be at risk.

What is the hazard associated with use of the product?

[X] Life-threatening (death has or could occur) due to the known sensitivity of dogs to sulfonamides compared to other domestic animals.
[X] Results in permanent impairment of a body function or permanent damage to a body structure
[X] Necessitates medical or surgical intervention to preclude or reverse permanent damage to a body structure or permanent impairment of a body function
[X] Temporary or reversible (without medical intervention)
[X] Limited (transient, minor impairment or complaints)
[X] No adverse health consequences
[ ] Hazard cannot be assessed with the data currently available

What is the likelihood of an adverse event occurring?

[ ] Probable
[X] Possible
[X] Unlikely
[X] Unknown

What are the potential immediate and long term consequences?

The potential immediate consequences have been well described in Appendix D and in the section on the overview section of adverse reactions to sulfonamide drugs in dogs and other animals and in humans from non-FDA sources. Depending on how sick the dog is prior to discontinuing the feeding of the dog treats, it may take a day or so up to slightly more than a month before many owners indicate their dog is back to normal. In dogs with Fanconi-like syndrome (which may not be directly related to sulfonamide drug exposure), it may take even longer than this to get urine protein, amino acids, electrolytes, ketones and glucose levels back to within the normal range. In a small percentage of dogs with a potential sulfonamide hypersensitivity reaction, it is possible that renal function may never return to normal. The long term effects of these potential sulfonamide hypersensitivity reactions, especially on the kidney, have not been well established in dogs.

CVM's AHHE Committee recommends the following:

a) Recall Classification: [21 CFR 7.41(b) and RPM 5-00-20 (j)].

1-Class I	[ ]	
2-Class II	[X] (Lot 2243HVB)	
3-Class III	[X] (other 4 lots)	
4-Market withdrawal	[ ]	Skip parts b through d.
5-Non-Concur	[ ]	Skip parts b through d.
6-Safety Alert	[ ]	Skip parts b through d.
7-Stock Recovery	[ ]	Skip parts b through d.

b) Depth of Recall: [21 CFR 7.42(b)(1) and RPM 5-00-20(k)].

1-Consumer or User Level	[X] (Lot 2243HVB)
2-Retail Level/Veterinarian	[X] (Lot 1304HVC)
3-Wholesale Level	[X] (other 3 lots)
4-NA	[ ]

c) Level of Effectiveness Checks:
- [X] Level A – 100% of the total number of consignees to be contacted for Lot 2243HVB
- [X] Level B – Greater than 10% but less than 100% of the total number of consignees to be contacted for the other 4 lots.
- [ ] Level C – 10% of the total number of consignees to be contacted.
- [ ] Level D – 2% of the total number of consignees to be contacted.
- [ ] Level E – No effectiveness checks.

d) Level of Audit Checks: [Investigations Operations Manual Chapter 7, Section 7.3.2.2]
- [ ] Level A – 100% of the total number of consignees to be contacted.
- [ ] Level B – Greater than 10% but less than 100% of the total number of consignees to be contacted.
- [ ] Level C – 10% of the total number of consignees to be contacted.
- [X] Level D – 2% of the total number of consignees to be contacted for all 5 lots.
- [ ] Level E – No effectiveness checks.

Narrative Summary:

A recall letter dated January 8, 2013 from Milo's Kitchen (Tim Cole, EVP Sales) asks each customer of the recalling firm (presumably (b) (4) distributors, (b) (4) retailers and (b) (4) military installations with the Dept. of Defense) to remove all sizes and lot numbers of the following 2 products from their shelves and destroy it via their reclamation process.

- All sizes of Milo's Kitchen brand Home-Style Dog Treats—Chicken Jerky

  3.3 oz. Universal Product Code (UPC) 0-79100-50471-8

  14 oz. UPC 0-79100-51077-1

  20 oz. UPC 0-79100-50468-8

- All sizes of Milo's Kitchen brand Chicken Grillers Home-Style Dog Treats—Chicken Recipe with natural smoked flavor

  3.3 oz. UPC 0-79100-51310-9

  14 oz. UPC 0-79100-51312-3

  20 oz. UPC 0-79100-51313-0

The recall was not for specific lot numbers, but for all products currently in commerce. The Chinese manufacturer ((b) (4)), produced (b) (4) cases of Chicken Jerky and (b) (4) cases of Chicken Grillers for a total of (b) (4) cases. (b) (4) cases of Chicken Jerky and (b) (4) cases of Chicken Grillers for a total of (b) (4) cases were shipped internationally ((b) (4)) by this manufacturer.

No information was provided on all the lot numbers affected by this recall. However, if we assume that the use-by-date is ~18 months (~78 weeks) from the date the product was ordered, the packaging date is (b) (4) after the product is ordered, it takes about (b) (4) to ship the packaged dog treats from the manufacturer in China to the (b) (4) and then from the

(b) (4) to the US, all the packaged dog treats en route to the US at the time of the recall never made it into domestic commerce in the US, this recall effectively went down to the consumer level, all out-of-date product had previously been removed from retail and dog owner shelves and destroyed, and all manufacturing in China of the 2 recalled products destined for the USA stopped on January 9, 2013, then this recall likely affected all uneaten Milo's Kitchen Chicken Jerky and Chicken Grillers that were destined for the US and packaged by (b) (4) from about July 16, 2011 (where the first 6 numbers and letters of the lot number would be 1197HV) to January 9, 2013 (where the first 6 numbers and letters of the lot number would be 3009HV) (see background section for details about the lot numbers). Since all lots had HV in the fifth and sixth position of the lot number, this recall likely affected lots with the following range in the first 4 numbers -- 1197 to 1365 and 2001 to 2366 and 3001 to 3009.

No information was provided on the quantity of the two products (Chicken Jerky and Chicken Grillers) that was returned to Del Monte, destroyed by the customer's reclamation process, or discarded by consumers.

This recall was initiated, to a large extent, by the findings of the State of New York Department of Agriculture and Markets (SNYDAM), who on January 7, 2013, informed the U.S. Food and Drug Administration (FDA) and the recalling firm that parts per billion (ppb) levels of six drugs had been found in 5 samples of Milo's Kitchen Chicken Jerky (sulfamethoxazole, trimethoprim, tilmicosin, enrofloxacin, sulfaquinoxaline, and sulfaclozine).

None of the subsamples tested for sulfamethoxazole (n=33) or for trimethoprim (n=63) contained quantifiable levels of these 2 drugs. Less than 10% of the subsamples tested for tilmicosin and enrofloxacin (n=63 for both drugs) contained quantifiable levels and the levels found were just barely above the limit of detection of the lab and well below tolerances established by the FDA in edible products from other species. Thus, four (sulfamethoxazole, trimethoprim, tilmicosin, and enrofloxacin) of these six drugs were not likely the cause of the adverse effects reported to FDA/CVM in consumer complaints, primarily from dog owners and veterinarians, associated with the feeding of the two recalled dog treats over the past several years.

Two of the six drugs (sulfaquinoxaline and sulfaclozine) were found in quantifiable levels in ≥33% of the subsamples tested (n=63 for both drugs) and 3 of the 63 subsamples contained combined levels of sulfaquinoxaline + sulfaclozine that exceeded 340 ppb. The highest 2 subsamples on a recovery corrected basis contained 3,710 and 3,770 ppb when the levels of both sulfonamide drugs were combined.

I then provided a review of the topics, noted below,

FDA approved uses and tolerances in chickens for sulfaclozine and sulfaquinoxaline.
Tolerances for all sulfonamide drugs in 21 CFR 556.
Negligible residues.
Overview of adverse reactions to sulfonamide drugs in dogs and other animals and in humans from non-FDA sources.
FDA approved doses and uses of sulfonamide drugs in dogs.

Following this, I compared (in Appendix D) the clinical signs and clinical pathology findings in the sulfadimethoxine (with and without ormetoprim) adverse drug experience reports over the past ~25 years to the clinical signs and clinical pathology findings in the consumer complaints of chicken jerky dog treats (reported to FDA/CVM from 2006 to mid 2010) and of sweet potato dog treats (2011 to May 2013).

With the exception of Fanconi-like syndrome, I would assess the overall clinical signs/clinical pathology findings associated with ADER with SDMX (with and without ormetoprim) to be somewhat to reasonably close to those reported in the chicken jerky and sweet potato dog treats. In addition, since FDA/CVM has received many reports of adverse effects within 48 hours (2 days) of first exposure and also many reports of adverse effects within 1 to 3 weeks (7 to 21 days) or even longer following the first exposure to the chicken jerky and sweet potato dog treats (personal assessment following review of the consumer complaints), I would assess the time course associated with adverse effects to be reasonably close to those reported with SDMX (with or without ormetoprim).

The major problem that exists in concluding that the adverse effects reported in the consumer complaints associated with Milo's Kitchen chicken jerky dog treats are caused by ppb levels (not corrected for recovery) of sulfaquinoxaline plus sulfaclozine (and/or sulfamethoxazole) is dose related. Since almost 89% (56/63 = 0.889 = 88.9%) of the Milo's Kitchen chicken jerky subsamples tested by SNYDAM FL contained LESS THAN 85 ppb of total sulfonamides (sulfaquinoxaline plus sulfaclozine plus sulfamethoxazole) on a recovery corrected basis, I believe there is a distinct possibility that the vast majority of the sulfonamide drug residues found are simply incidental findings and are not the cause of the reported adverse effects.

In any event, when dealing with the scientific uncertainty, especially regarding dose, which abounds with potential hypersensitivity reactions, I believe it is best to find solid scientific ground and use safety factors and practical worst case scenarios to determine the cutoff points for a Class I, II and III recall. Two 90-day oral toxicity studies with sulfaquinoxaline in beagle dogs were located in [Veterinary] Master File (b) (4) and provide the solid scientific ground upon which to determine these cutoff points.

Following a detailed review of these 90-day oral toxicity studies in beagle dogs and the use of safety factors and practical worst case scenarios, I recommend the following cutoffs for a class III, II and I recall for pet treats likely to be consumed by dogs. These cutoff values are for the combined, recovery-corrected sum of dog treats that contain only quantifiable levels of sulfaquinoxaline or contain quantifiable levels of sulfaquinoxaline and quantifiable levels of one or more additional sulfonamide drugs [designated as sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) hereafter]. These recommendations were developed to assist the CVM/Division of Compliance in handling situations where multiple sulfonamide drugs are present on the MKCJ and are based on the assumption that the toxicity of sulfonamide drugs are additive.

Note: These recommendations only apply to determining the recall class for total sulfonamide residues when quantifiable levels of sulfamethoxazole and/or sulfaclozine are found in combination with quantifiable levels of sulfaquinoxaline. These recommendations in no way inhibit CVM from taking regulatory action if a quantifiable level of sulfamethoxazole were found on the chicken jerky treats since there is no tolerance established for this drug in the USA or if the sulfaclozine residues on the chicken jerky treats exceed the zero tolerance established in 21 CFR 556.625 for uncooked edible tissues of chickens even if the total sulfonamide levels are below a recommended cutoff value.

If all subsamples tested in the lot contain less than or equal to 340 ppb of sulfaquinoxaline plus sulfaclozine plus sulfamethoxazole, then no recall is necessary.

A class III recall would be any lot of chicken jerky where the combined recovery corrected levels for quantifiable residues of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) in one or more dog treat(s) exceed 340 ppb but are less than or equal to 1.25 ppm (1,250 ppb). This product is not expected to cause adverse health consequences.

A class II recall would be any lot of chicken jerky that contains one or more dog treat(s) with more than 1.25 ppm (1,250 ppb) and less than or equal to 15.0 ppm (15,000 ppb) of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) on a recovery corrected basis as long term use of, or exposure to this product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

A class I recall would be any lot of chicken jerky that contains one or more dog treat(s) with more than 15.0 ppm (15,000 ppb) of sulfaquinoxaline plus sulfaclozine (plus sulfamethoxazole) on a recovery corrected basis as there is a reasonable probability that the long term use of, or exposure to, this product will cause serious adverse health consequences or death.

All 5 lots of Milo's Kitchen chicken jerky (MKCJ) contained one or more drug residues that could be considered a violation of the Federal Food, Drug and Cosmetic Act as amended. For 4 lots (1320HVC and 1325HVC and 1272HVA and 1304HVC) this violation could potentially lead to a class III recall. For lot 2243HVB, this violation could potentially lead to a class II recall.

Finally, it is important to recognize that the 5 samples analyzed by the SNYDAM FL were collected off the shelf at retail and were not known to be associated with any consumer complaints to FDA/CVM or SNYDAM at the time of collection. Only one of the five lots of (MKCJ) that were analyzed by SNYDAM FL has been mentioned in a consumer complaint sent to the FDA after the sample was collected and this lot was 2243HVB.

FDA did receive FACTS consumer complaint #130206 on January 16, 2013 where a 14-year-old male neutered cockapoo developed diarrhea, excessive thirst, frequent urination, and urinary incontinence after consuming 4 MKCJ treats per day for about 6 months. MKCJ lot number 2243HVB came from a 23 [likely meant 20 or 3.3] oz plastic bag that was purchased in December 2012 and appeared to be the lot fed immediately prior to and during the time the clinical signs were noted. On January 16, 2013, the complainant indicated the dog had shown the clinical signs noted above for weeks and that the dog was taken to a veterinary clinic about 1 month ago and blood tests showed loss of kidney function. It is worth noting that the two subsamples, out of the 63 tested by SNYDAM FL, which contained by far the highest levels of both sulfaclozine and sulfaquinoxaline, came from lot 2243HVB.

The FDA has reviewed the analytical results from SNYDAM FL and found them to be acceptable.

The animal population at greatest risk would be sulfonamide sensitive dogs. Sulfonamide sensitive humans that consume some of these dog treats could also potentially be at risk. The hazard associated with the product ranged from no adverse health consequences to potentially life threatening consequences in sulfonamide sensitive dogs. It needs to be recognized that there is incomplete data concerning the dose needed to cause an adverse effect in sulfonamide sensitive dogs when this hazard assessment was made.

The likelihood of an adverse effect occurring was judged as possible for lot 2243HVB. The likelihood of an adverse effect was judged as unlikely for lot 1304HVC (since 1 of 23 subsamples contained total sulfonamide levels on a recovery corrected basis of 1.117 ppm) and none to very

unlikely for lots 1320HVC and 1325HVC and 1272HVA based on the SNYDAM FL results. However because of the incomplete data, it is possible that other scientists may assess the likelihood of an adverse effect as unknown.

Depth of a recall will vary by lot. It is recommended to the consumer level for lot 2243HVB, to the retail level/veterinarian for lot 1304 HVC, and to the wholesale level for lot 1272HVA and lot 1320HVC and lot 1325HVC.

The FDA/CVM Animal Health Hazard Evaluation Committee concurs with the San Francisco District Office in regards to their recommendations for a Level A (100%) effectiveness check and a Level D (2%) audit check for the recalled products.

Animal Health Hazard Evaluation Committee

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Neal Bataller, ME, DVM, Chair

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Sharon Benz, Ph.D., PAS

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Dr. Terry Proescholdt, Leader, Feed Safety Team

Prepared by:

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Randall A. Lovell, DVM, PhD, DABVT

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