National Drug Residue Milk Monitoring Program

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CHAPTER 03 - FOODBORNE BIOLOGICAL HAZARDS

10-01-97

National Drug Residue Milk Monitoring Program

(FY 98-00)

09-30-00

09C[][]0903039 (Grade A)

71008 (Non-Grade A) *

FIELD REPORTING REQUIREMENTS

1. **Hard copy Reporting**

   Submit hard copy of all investigational reports, both state and Federal, relating to illegal drug use, distribution or labeling to CVM (HFV-246) for headquarters review and compilation of data.

   Submit hard copy of all investigational reports, both state and Federal, relating to the contamination of milk offered for sale, the disposition of any adulterated milk, regulatory actions taken against the producer, or any subsequent seller of adulterated milk to CFSAN, Division of Cooperative Programs, HFS-625.

2. **Reporting of Analytical Results**

   Denver laboratory will report all results in LMS, use the LMS Compliance Data Reporting System Antibiotics in Feeds and Foods Screen form code ANT, PAC 03039 for Grade A milk and PAC 71008 for non-Grade A milk. Use form code KIT for test kit analysis only - the some PAC assignments described above apply. In addition, Denver will provide a weekly summary of analytical findings to CFSAN, Division of HACCP, Laboratory Quality Assurance Branch (LQAB), HFH-450. LQAB will distribute this data to CFSAN, Domestic Programs Branch, HFS-636 and the States submitting samples. States will enter this data in the National Drug Residue Database.

States will report all results for the initial analysis of samples they analyze on Attachment A, and any subsequent samples for either confirmation of initial results or identification of violative producers on Attachment B. Investigations due to positive findings by the state central laboratories should be reported on Attachment C.

3. **Sample analyses that result in no residue detected**

    a. States participating in this program will submit all analytical results weekly to Laboratory Quality Assurance Branch, HFH-450, FAX: 708-728-4120 on laboratory report forms furnished by LQAB. (see Attachment A - Sample Collection Report/Laboratory Results Report form).

    States will also transmit a copy of the record of the Sample Collection Report/Laboratory Results Report (Attachment A) to accompany samples submitted to FDA Denver laboratory. This record should be completed to include the Sample Collection Report (upper half) of the form. If any prior testing has been completed on the sample by the state, the lower half (Laboratory Results) of the form should be completed.

    b. DENVER's weekly summary should include the following: sample #; collection date; site; and results (drug and level) for all analyses to HFH-450 for compiling. HFH-450 will transmit this information weekly to CFSAN/Domestic Programs Branch, HFS-636, and the state laboratories submitting samples and to the National Drug Residue Database monthly. FDA Headquarters contacts are: Domestic Programs Branch, HFS-636, FAX (202) 205-9670, (202) 205-4771, Milk Safety Team, HFS-626, FAX: 202-205-5560, Division of Field Science, HFC-140, FAX: 301-443-6388, Division of Federal-State Relations, HFC-150, FAX 301-443-2143, and CVM Office of Surveillance and Compliance, HFV-200, FAX: 301-594-1807.

4. **Residues at or above the limit of detection but not exceeding the safe or tolerance level**

    a. DENVER will report as indicated in 3.b. above.

    b. Milk Safety Team will notify state milk regulatory agencies, CVM, ORA, and respective FDA regions and districts, via form letter (see Attachment E), of any findings verified above the level of detection.

5. **Residues EXCEEDING safe or tolerance level**

    a. States participating in this program will report positive results on Attachment A (Sample Collection Report /Laboratory Results Report Form), and will report follow-up actions, trace backs to the violative producer(s), etc. on Attachment B (Initial Drug Residue/Laboratory Results Report). States will initiate regulatory action against milk represented by all samples for which the analysis they performed indicated the presence of a drug residue above safe level or tolerance (see Part IV, page 2) for those methods having FDA acceptance. States will also complete an investigation report

(Attachment C - Report of Investigation Due to Positive Laboratory Results for Drug Residues) for all investigations performed pursuant to positive results from this program. All state reports will be directed to HFH-450 through the district or Regional Milk Specialist. Copies of Attachment C will be sent to HFV-236 by HFH-450.

DENVER will immediately report positive findings, * after check analysis have been completed * to HFH-450 as indicated in 3.b. above. HFH-450 will immediately transmit this information to: FDA, Milk Safety Branch, HFS-626 and the state laboratory submitting the sample. Follow up samples will be collected as necessary to identify the producer. HFH-450 will transmit information relating to this program to the National Drug Residue Database monthly.

HFH-450 will also FAX the above information to the respective RMS and the respective state milk regulatory official submitting the sample.

b. CVM (HFV-200) will review documents and initiate follow-up, if warranted, relating to drug sales, prescription, or use.

c. Milk Safety Team (HFS-626) will review document(s) and initiate follow-up, if warranted, relating to milk through ORO (DFSR, HFC-152) and/or CVM.

d. DFSR (HFC-150) will notify respective FDA regions and districts (See Part V). The Regional Milk Specialist will notify the state milk regulatory agency.

6. **Other Reporting**

At the time of sampling, the investigator is requested to collect information from the plant that specifies the total number of loads, the total volume in pounds of milk received the week prior to the sample being collected, the grade of milk contained in the truck, the identity of the finished product the milk will most likely be used for, and the identity of the producers contributing to the bulk milk pickup tanker sampled. This information is to be directed to HFH-450 on the Sample Collection Report/Laboratory Results Report Form. (see Attachment A)

PART I - BACKGROUND

The Food and Drug Administration (FDA) has primary responsibility for regulating most foods, including milk, shipped in interstate commerce. FDA's milk safety program relies on participation by state regulatory agencies. This participation is described in a 1977 Memorandum of Understanding (MOU) between the National Conference on Interstate Milk Shipments (NCIMS) and the FDA and is designed to provide assurance of a clean and safe national milk supply. The FDA, with the support of the NCIMS initiated the National Drug Residue Milk Monitoring Program (NDRMMP) in February 1991. The NDRMMP is designed to assist and supplement the longstanding NCIMS program.

The NDRMMP is designed to provide an indication of animal drug residues that may be present in milk and the extent that farmers, distributors, and veterinarians comply with the Federal Food, Drug, and Cosmetic Act, implementing regulations and applicable policies. In the past, the NDRMMP involved, in part, the analyses of raw milk samples in FDA laboratories. This revision will continue to utilize FDA laboratories for the analyses of raw milk samples and will add "quick screening" analyses by state laboratories certified by the Office of Field Programs, Laboratory Quality Assurance Branch, HFH-450.

Three states will be scheduled to submit five samples each week of the fifty week program. This will result in 750 samples being analyzed by the FDA/Denver laboratory.

The "quick screening" analysis by the states will add approximately an additional 5,000 analysis to the results obtained from the FDA laboratory and will encourage the use of these methods by the states as they become accepted for use by FDA. An important benefit of the NDRMMP is the transfer of analytical technology from FDA to state and industry laboratories and then the transfer of improvements and refinements among all participating laboratories.

The analytical findings from the NDRMMP should not be used to compare the raw milk in one state with that in another state. Raw milk moves in interstate commerce for processing and retail sale, and the actual state source might be erroneously assumed.

The results from the NDRMMP will help in the design of future education and compliance efforts for use by Federal, state, and local authorities. This initiative will enhance the NCIMS (PMO - Appendix N) residue testing program and provide information on which to focus regulatory priorities.

PART II - IMPLEMENTATION

A. **OBJECTIVES**

- To provide an indication of the animal drug residues that may be present in milk.
- To provide an indication through follow-up investigations of the extent that farmers, distributors and veterinarians comply with Federal regulations concerning the proper distribution, sale and use of drugs in dairy cattle.
- To assist Federal, state and local milk officials with information regarding drug residues in milk for designing educational and enforcement programs.
- To facilitate the transfer of analytical methods/technology from FDA to state and industry laboratories.

B. **PROGRAM MANAGEMENT**

- Approximately *5000* samples are to be collected from selected farm milk, bulk tank trucks. These samples will be selected from those samples now being collected by the states in their monitoring of industry testing pursuant to the Grade A Pasteurized Milk

Ordinance (PMO) Appendix N. Of these, 5000 samples will be analyzed by the participating states using materials furnished by FDA. This analysis by the states will occur in state milk laboratories and will be performed by an analyst certified following the procedures of the U.S Department of Health and Human Services, Evaluation of Milk Laboratories, 1995 edition. 750 samples will be submitted to FDA/Denver for analysis as described in Part IV of this program.

- LQAB will prepare and furnish CFSAN/Domestic Programs Branch, HFS-636, with a monthly schedule, prepared at least one month in advance, showing the number of analyses to be performed, by state, and the number of samples, by state, to be submitted to the FDA laboratory.

PART III - INSPECTIONAL

A. SAMPLE COLLECTION

- Following the provisions of Appendix N of the PMO, each state is required to conduct quarterly audit checks of plants, receiving and transfer stations. Milk is to be collected from a minimum of 10% of the tankers that come to that location on the day the audit is performed.
- The LQAB will contact the appropriate state milk laboratory officials who will receive samples at the state laboratories, and will notify them of the number of samples to analyze each week (using the quick screening methods), and the number of samples to be forwarded to Denver. This schedule will be furnished the state at least 30 days prior to the sample collection date.
- The LQAB will contact the appropriate RMS for assistance in notification of the state milk regulatory official(s) who will collect or supervise the collection of the sample(s) during the specified sampling period. This notification will be furnished the state at least 30 days prior to the sampling period.
- The sample item is raw milk collected from bulk milk pickup tankers prior to unloading.
- Three six-ounce (180 ml) subsamples of milk constitute a sample.
- Failure to submit a sample as scheduled will necessitate the rescheduling of the collection on a date to be specified by LQAB.
- Samples to be submitted to the state laboratories for screening in this program will be investigational. Sample Collection Report/Laboratory Results Report Forms, Initial Drug Residue Report/Laboratory Results Report Forms, Report of Investigation Forms, Test Kit Problem Sheets, and FDA DENVER Laboratory State Request for Special Analysis will be provided to the states by LQAB (Attachments A, B, C, D, and F).
- All samples to be submitted to Denver will be investigational and one report form (Attachment A) will be prepared for each sample.
- The completed Attachment A is to include:

- date sample obtained;
- location from which the sample was obtained;
- the name and address of the truck firm;
- the truck permit number;
- the name and address of each bulk milk pickup tanker;
- grade(s) of milk contained in the truck. In cases of commingled loads, indicate the amounts (in pounds)contributed from grade A and non-grade A farms;
- identification of the finished product the milk will most likely be used for, e.g., cheddar cheese or bottled milk.

- Containers and overnight mailers will be provided by LQAB to the state laboratories that will be forwarding samples to Denver. Samples should be submitted to Denver in a timely manner (to arrive at Denver no later than *Wednesday* of collection week).

B. **SAMPLE SUBMISSION**

- The LQAB after consulting with the FDA Denver laboratory, will determine the number of samples and will determine which states will submit samples each week to the FDA Denver laboratory. LQAB will notify states and CFSAN/Domestic Programs Branch, HFS-636 either by phone or FAX. States will send LQAB a Sample Collection and Laboratory Results Form(s) (see Attachments A and/or B) at the same time they submit samples to the Denver laboratory.
- All samples found positive on a screening assay for chloramphenicol by states are to be forwarded to the Denver Laboratory for confirmation.
- Each week 3 states will ship 5 samples each to the Denver laboratory. This will result in 750 samples/year to be analyzed by Denver Laboratory.
- In addition, all positive results from screens performed by the state central laboratories using any non-official PMO methods can be sent to the Denver laboratory for further verification.
- LQAB will provide collection reports, packaging and shipping materials, laboratory reporting forms and directions for obtaining the samples to the appropriate state officials. The Denver laboratory will return packaging and shipping materials to the appropriate state lab.
- The samples are to be collected aseptically, in accordance with both **Standard Methods for Examinations of Dairy Products, APHA**, Chapter 4, Sampling, and the FDA **INVESTIGATIONS OPERATIONS MANUAL**, Subchapter 426, Aseptic Sample, in 6 oz. plastic bags, or other acceptable containers. The samples are to be packaged on blue ice, shipped cold *(samples may be frozen)*, and given immediately to a carrier for overnight delivery service. **SAMPLES MUST ARRIVE AT THE**

DENVER LAB MONDAY, TUESDAY, OR WEDNESDAY TO FACILITATE SAMPLE ANALYSIS.

NOTE:BECAUSE OF STATE BUDGETARY CONSTRAINTS, IT MAY BE NECESSARY FOR THE RMS TO ARRANGE FOR AN FDA CSO/CSI TO COLLECT THE ASSIGNED SAMPLES IF THE STATE IS UNABLE TO DO SO.

Please address samples to:
Food and Drug Administration
Denver Federal Center
Attn: Sample Custodian
Building 20, Entrance 10 W
6th and Kipling Streets
Denver, CO 80225-0087
Phone (303) 236-3062

- The Denver laboratory will plan work so that they can assay *fifteen* samples per week, and report findings weekly.
- The state laboratory shipping the sample is to telephone the *Denver Veterinary Section Supervisory Chemist (currently vacant) at (303) 236-3062, backup contact is Emma R. Singleton, Laboratory Director, (303) 236-3060* of the shipment and provide a telephone contact number. This will permit Denver to notify the shipper of the need for recollection of the sample in the event sample breakage or spoiling occurs. Denver, upon receipt of the milk samples, should check and record temperatures for each sample. For any sample exceeding 40° F (or 4.4° C), Denver will notify the contact person of the need for recollection.

C. **INVESTIGATION REPORTS AND ESTABLISHMENT INSPECTION REPORTS (EIR's)**

Reports of investigations by FDA initiated in response to the Enforcement Plan will be prepared by the Federal investigator. Reports will be completed as expeditiously as possible and sent to the respective Regional Milk Specialist (RMS). The RMS will review the reports and forward them to appropriate supervisory investigators and/or compliance branch staff, to issue further inspectional requests as necessary.

Reports of Investigations Due to Positive Laboratory Results for Drug Residues (see Attachment C) completed by states will be, as soon as possible, sent to the respective RMS (See Field Reporting Requirements, section 6).

Both FDA and state laboratories should use Attachment D to report problems and or inconsistencies with the rapid test kits. Forward Attachment D forms to:
CVM, MPN II
Attn: Dr. Norris Alderson, HFV-500

7500 Standish Place
Rockville, MD 20855

PART IV - ANALYTICAL

- The state central laboratory will test one of the sub-samples from each of the samples collected using test kits supplied by FDA and send the information collected to the LQAB. This will result in a total of 5,000 analyses.
- The other two sub-samples from this set will be either sent to the FDA laboratory in Denver, or will be discarded if the state analysis was negative and the sample was not scheduled to be sent to Denver. 750 samples will be scheduled to be sent to the Denver laboratory.
- FDA Denver laboratory will analyze *15* samples each week for a period of 50 weeks. *750* samples will be analyzed during the course of the year by the Denver laboratory. * Denver will only analyze samples received below 4.4 degrees C and in good condition. *

  - Each week three states will be scheduled to ship 5 tanker samples to the Denver laboratory. Three 6-ounce subsamples will be collected from the tanker, two, 6-ounce subsamples will be aseptically commingled and transferred to 6-ounce plastic bottles/bags prior to shipment to the Denver laboratory for analysis. One 6-ounce subsample will be retained by the state for analysis.
- When necessary, follow-up samples/analyses to be verified or confirmed will be assigned to Denver or other FDA laboratories. (See Part III, page 2 regarding chloramphenicol.)
- FDA will analyze milk samples using FDA-accepted methods. These FDA-accepted methods will include Green Book, AOAC, and other methods/screening tests found acceptable to FDA.
- The following analytical scheme will be employed to verify specific animal drug residues:

  Original analysis (charm screening kits) performed at the sensitivity given for the analytes of interest and positive findings on the screening will be identified (verified) and quantitated using the check procedure. The analytical values reported for the check (or quantitation procedure) must be above the established limit of quantitative for the procedure given.

  Original analyses that cannot be verified by a check analysis will be reported as negative.

  - Denver will also include quality controls, sample blank and fortified sample (at or above target level) with each series of milk samples.
- Assays for the following drugs are to be carried out under the NDRMMP. Assays for other drugs may be added during the year. Methods will be available upon request to the Center for Veterinary Medicine. Safe/tolerance levels are listed below.

DRUG	SAFE/TOLERANCE LEVEL(ppb)
Chloramphenicol	[1]
*Florfenicol	10*

DRUG	SAFE/TOLERANCE LEVEL(ppb)
Chlortetracycline	30
Oxytetracycline	30
Tetracycline	80
Sulfachloropyridazine	10
Sulfadiazine	10
Sulfadimethoxine	10(21 CFR 556.640)[2]
Sulfamerazine	10
Sulfamethazine	10
Sulfapyridine	10
Sulfaquinoxaline	10
Sulfathiazole	10
Novobiocin	100(21 CFR 556.460)[2]
Ivermectin	2
Clorsulon	200

[1] No level of chloramphenicol is acceptable

[2] Tolerance level

A. **FDA METHODS OF ANALYSIS AND DRUG LEVEL VERIFICATION**

1. **Chloramphenicol**:
   a. Original Analysis - CHARM II
   b. Check Analysis - Laboratory Information Bulletin (LIB) 3529
2. **Sulfonamides**:
   a. Original analysis - *CHARM II*
   * The sensitivity of CHARM II for the Sulfa drugs of interest are as follows:
   Sulfadiazine - 4 ppb
   Sulfadimethoxine- 4 ppb
   Sulfamethazine- 10 ppb
   Sulfathiazole- 8 ppb *
   * **Note**: At laboratory's option, TLC, LIB 3528 can be used as a check identification. *
   b. Check analysis - Smedley, Weber HPLC method *(revision 3/16/92 (8/10 sulfas)).*

NOTE: When the analysis of a milk sample collected, at random, under the NDRMMP indicates the presence of more than one sulfonamide, the laboratory will identify and quantify each sulfonamide.

3. **Tetracyclines** (TC, CTC, OTC):
    a. Original analysis - *CHARM II* * The sensitivity of CHARM II for the tetracyclines of interest are as follows:
    Chlortetracycline- 24 ppb
    Oxytetracycline- 24 ppb
    Tetracycline- 6 ppb *

    b. Check analysis: CVM's HPLC Method,
    * JAOAC, Vol.76, No.2 (1993) p. 329- 334 *
4. **Novobiocin**:
    Original and check analysis - * JAOAC, Vol. 71, No. 4, 1988, p. 776-778. *
5. **Ivermectin**:
    Original and check analysis - LIB 3461.
6. Clorsulon:
    a. Original and check analysis - LIB 3038, * J. Liq. Chrom., Vol.16, No. 2 (1993), pp. 513-520. *

* **Note**: Novobiocin, Ivermectin, and Clorsulon will be analyzed quarterly. *

7. ***Florfenicol**:
    a. Original analysis - CHARM II * (CHARM II is sensitive to approximately 25 ppb for Florfenicol). *
    b. Check analysis - CVM's HPLC Method *(Version 11/7/96 w/ Schenck modification of 8/28/97)*
8. **CONFIRMATION OF DRUG RESIDUE IN SAMPLES COLLECTED UNDER THE ENFORCEMENT PLAN**

    All positive results obtained from the 750 FDA samples submitted by the states will be subject to confirmation. Except in the case of positive results for chloramphenicol (see Part III, page 2, B), it is not necessary to confirm positive results from the 5000 state samples analyzed by the states using official PMO methods.

    1. **Chloramphenicol**: For all samples collected under the Enforcement Plan, analyzed by FDA and determined to contain chloramphenicol, the identity will be confirmed using CVM's "Procedure For Confirmation of Chloramphenicol Residues in Bovine Milk Using GC/MS," Kijak (5/9/91).

2. **Sulfonamides and Tetracyclines**: For all samples collected under the Enforcement Plan, analyzed by FDA,and determined to exceed the safe or tolerance level for Sulfonamides and or Tetracyclines, the identity of these residues may be confirmed by CVM's Office of Science should confirmation be required. Submit these sample to:

   *Food and Drug Administration
   Attn: Michael Thomas, HFV-510
   Division of Residue Chemistry
   8401 Muirkirk Road
   Laurel, MD 20708*

   Notify Mr. Thomas *((301) 827-8020)* of all pertinent shipping information.

3. **Novobiocin**: No confirmatory method available at this time.
4. **Ivermectin**: For all samples collected under the Enforcement Plan, analyzed by FDA, and determined to exceed the safe or tolerance level for Ivermectin, the identity will be confirmed using CVM's "Procedure for the Confirmation of Ivermectin Residue in Milk by Liquid Chromatography/Particle Beam Mass Spectrometry," Heller (10/26/92).
5. **Clorsulon**: For all samples collected under the Enforcement Plan, analyzed by FDA, and determined to exceed the safe or tolerance level for clorsulon, the identity will be confirmed using the Merck Sharp Dohme method, "Confirmatory Assay for Identifying Clorsulon Residues in Milk" (MK-0401).
6. ***Florfenicol**: For all samples collected under the Enforcement Plan, analyzed by FDA, and determined to exceed the safe or tolerance level for florfenicol, the identity of the residue may be confirmed by CVM's Office of Research, should confirmation be required.*

   Selection of the appropriate laboratory to perform confirmatory analysis will be based upon the residue(s) involved and the availability of appropriate instrumentation and/or trained personnel. Contact the ORA/Division of Field Science for assistance in identifying a lab for confirmation.

9. **REPORTING REQUIREMENTS**

   Follow reporting requirements indicated on program cover sheet. Weekly reports of all analyses are to be FAXED to the Laboratory Quality Assurance Branch, HFH-450.

10. **LABORATORY QUALITY ASSURANCE PROGRAM**

    ORA/Division of Field Science and CFSAN/Laboratory Quality Assurance Branch will jointly, three times each year, implement a Quality Assurance Program to cover the residues analyzed under this program.

    The quality assurance samples will be prepared by the Baltimore District Laboratory.

This Quality Assurance Program for the National Drug Residue Milk Monitoring Program (QAP-NDRMMP) is a segment of the National Check Sample Program (NCSP) which is a portion of the total FDA/ORA quality assurance effort. It involves the analysis of samples representative of those analyzed under the NDRMMP by the laboratory(ies) identified in the program.

Objective

The QAP-NDRMMP is designed to:

- ensure that all analyses performed under the NDRMMP are done in accordance with the methods specified within the program;
- evaluate the analytical capabilities of the analyzing laboratory(ies) and quality of evidence documentation with respect to regulatory actions; and
- identify and resolve problems that this program may uncover.

Samples and Methodology

Samples analyzed under this program will consist of milk and milk products regulated under the PMO. The samples will be prepared to represent the drug residues identified in the NDRMMP. Incurred residues will be used whenever possible.

For those residues where official methods for their detection have not been finalized, the issuance of QA samples containing these residues, will be considered on a case-by-case basis. *Level: The fortification level for the sample prepared as the quality assurance sample should be approximately 1.5 X [X= safe or tolerance level of the residue in question]. *

Methods: The methods used in the sample analysis under this program will be those identified in the Analytical Section of the NDRMMP. The issuing laboratory will use "official" methods for testing the sample before it is issued. The appropriate Denver laboratory group; DENVAS or the Micro Section, will use those methods (LIB, test kits, etc.) used to test regulatory samples collected under this program.

Implementation: Issuance and Sample Analysis

DFS has the principal responsibility for managing this program and will coordinate the selection and distribution of samples.

Samples will be issued to the laboratory(ies) identified in the NDRMMP three (3) times in any given fiscal year and will encompass as many of the residues identified in the NDRMMP as practical.

DFS will work with the issuing laboratory, BLT-DO Laboratory, to determine which product (milk or milk products), residue(s) and residue level will be analyzed.

The issuing laboratory will perform a preliminary analysis (in triplicate) of the sample using the proper method and report the results to DFS. DFS will evaluate the acceptability of the preliminary analytical data obtained by the issuing laboratory. If the data is acceptable, then

the sample(s) will be forwarded to the participating laboratory(ies).

The laboratory(ies) identified in the NDRMMP will examine the sample according to this program, advance instructions and/or instructions accompanying the sample. Quality assurance samples are subject to all of the requirements found in the Laboratory Procedures Manual and the NDRMMP. All worksheet documentation shall be recorded in the format required for a violative sample. This includes complete analyst worksheet attachments and sample summaries.

Due to the fact that initial tests used in the NDRMMP, are "screening tests", when positive samples are encountered, they will be further analyzed in the same manner as "regular" or "routine" positive samples.

The analyst worksheet **must** be accompanied by a Sample Summary (FD-465), signed by the supervisor who will state the laboratory conclusion and give a laboratory classification based on the original analysis.

Reserve samples should be retained until notice is given that they may be destroyed.

Reporting Analytical Results

The analytical package will be forwarded to DFS for evaluation whithin thirty (30) calendar days after receipt of the sample. As necessary, because of holidays or the nature of the analyses, exceptions to this 30-day time frame will be noted in the written instructions regarding the sample. Any justifiable request for an extension of the established due date should be directed to the Scientific Coordinator identified as DFS contact in the program.

Evaluation of the Analytical Package

The analytical package will be evaluated by DFS and BLT-DO with respect to the full requirements contained in the program and in the written instructions accompanying the samples.

Identified problems will be brought to the immediate attention of the analyzing laboratory for corrective follow-up.

A final evaluation will be prepared and issued by DFS within forty-five (45) calendar days after the receipt of the analytical package.

PART V - REGULATORY/ADMINISTRATIVE FOLLOW-UP

ENFORCEMENT PLAN (EP)

The EP is for use when a residue in grade A or non-grade A milk exceeds the tolerance or the safe level (as stated in Part IV, page 2) when analyzed using FDA - accepted methods. In addition, this EP will be used when a sample is positive when analyzed using official PMO methods.

This EP provides FDA district offices with guidance on enforcement action against adulterated milk and the illegal distribution, sale, and use of a drug that caused a residue. The EP is recommended for implementation with agreement by CVM, ORA, and CFSAN based on review of the analytical findings. Milk Safety Team, HFS-626, will be responsible for the overall coordination and monitoring (in cooperation with the Division of Enforcement and Programs, HFS-605) of all regulatory activity involving milk. The regulation of milk is under the purview of CFSAN, and the regulation of drugs is under the purview of CVM.

A. **ADULTERATED MILK - The NCIMS-FDA Action Plan**

Under the MOU between the NCIMS and the FDA, states are responsible for the initial enforcement response to the incidents involving grade A milk. In addition, if the state can take action against non-grade A milk, FDA will cooperatively work with the state to effect enforcement action(s).

For state-collected samples, the RMS will arrange for contacting the State official to learn the planned action and request a copy of the plan. The state will share its milk enforcement plan with the RMS. The RMS will consult with the CFSAN Laboratory Quality Assurance Branch (LQAB) and the state milk sanitation agency and make a determination regarding the capability of the state laboratory to analyze raw milk, including methods, and determine if FDA assistance will be required. The RMS will notify DFS and the appropriate home district of a state request for analytical help. FDA will consider its analytical work-load to determine whether to assist the state or recommend another course of action. It is anticipated that the state will include its proposed action in its enforcement plan and undertake the follow-up outlined below.

When a sample contains a residue above the tolerance or the safe level (as stated in Part IV, page 2) or is positive when analyzed using an official PMO method:

- The milk from all the producers that contributed to the load will be individually sampled and tested within 72 hours of the positive analysis or notification by FDA of an analytical result above the safe or tolerance level. The producer samples will be taken by either the state agency or FDA, depending upon who took the initial tanker sample. This sampling will be coordinated by the FDA Regional Milk Specialist.

  In order for official samples to be obtained for use as a basis for FDA compliance actions against the culpable parties involved in the sale, distribution and/or use of drugs resulting in residues, 3-six-ounce sub-samples of milk should be obtained from each producer which contributed to the positive load. Two of these sub-samples will be submitted to the Denver laboratory, and one reserved for the state's analysis (if performed).
- Based on results of analysis, trace the source of the adulterated milk to a specific producer.
- Advise the RMS of the responsible producer(s) as soon as determined so that the cause of residue in milk can be investigated. The FDA investigation of drug distribution, sale and use may be carried out in conjunction with the state action. The RMS will keep CFSAN, CVM,

ORO, regional and district offices informed of important developments on a weekly basis to help coordinate investigations, analyses and enforcement.

B. **ADULTERATED MILK - The FDA Action Plan**

This section provides FDA districts with guidance on responding to a finding of residue above the tolerance or the safe level in grade A or non-grade A milk, or positive results from official PMO methods when state or local officials are not able to take appropriate action.

1. When a sample contains a residue(s) above the tolerance or the safe level or positive results from official PMO methods, the milk from all the producers that contributed to the load will be individually sampled by the state (if the state took the original sample) or the FDA, within 48 hours of receipt of the results of analysis, and tested by the FDA and state (if the state chooses to do this analysis).
2. Based on results of analysis, trace the source of the adulterated milk to the specific producer.
3. If the sample was collected by the state, the region or district will advise the appropriate state milk control agency of the responsible producer(s) as soon as determined. The FDA investigation of drug distribution, sale and use may be carried out simultaneously.
4. FDA districts should contact the CFSAN/Division of Enforcement and Programs, Case Processing Branch, HFS-607, for assistance in determining appropriate sample sizes and numbers of samples to be collected if dairy products (e. g., non-fat dry milk) have been manufactured from adulterated milk.

C. **ADULTERATED MILK - FDA Reports**

The RMS will report weekly any significant findings such as analytical results and involvement of FDA in investigations or sample analyses including numbers of milk samples expected to arrive at Denver for analyses. The RMS reports are to reflect the progress of the investigations and, if possible, to forecast resource needs and completion dates for each part of the follow-up.

D. **FDA REGULATORY RECOMMENDATIONS**

Recommendations for enforcement action regarding adulterated milk or dairy products manufactured from adulterated milk should be submitted to the Division of Enforcement and Programs, Chief, Case Processing Branch, HFS-607.

E. **ILLEGAL DISTRIBUTION, SALE OR USE OF A DRUG - FDA Plan**

The follow-up by FDA will employ routine procedures that may lead to investigations of producers, veterinarians, mobile drug peddlers, and others.

Investigative instructions can be found in Compliance Program 7371.002. Legal sanctions such as injunction, prosecution, seizure and warning letters are available. Compliance Policy Guide 7125.05 offers guidance in the investigation of illegal drug residues in meat, milk and

eggs. Recommendations for enforcement actions regarding illegal distribution, sale, or use of drugs are to be submitted to CVM, Case Guidance Branch, HFV-236.

The reporting by FDA districts will also follow routine procedures. States may freely adopt the FDA compliance program guidance.

PART VI - REFERENCES, ATTACHMENTS, AND CONTACTS

A. REFERENCES

1. Interstate Milk Shippers (IMS) list of Grade A Processors.
2. State list of names and locations of plants processing milk not under the Grade A IMS program.
3. Green Book of Methods.
4. **Standard Methods for the Examination of Dairy Products**, APHA.
5. **Investigations Operations Manual** (IOM).
6. **Compliance Policy Guide 7125.05** - Responsibility for Illegal Drug Residues in Meat, Milk and Eggs.
7. **Official Methods of Analysis of the Association of Official Analytical Chemists**, 16th ed., 3rd revision, 1997.
8. **Animal Drug Analytical Manual**, FDA/AOAC, 1985.
9. Compliance Programs
   7371.002 - Illegal Sales of Vet. Rx Drugs.
   7371.006 - Illegal Drug Residues in Meat and Poultry.
10. **Code of Federal Regulations**, 21 CFR Parts 500-599.
11. **U.S. Department of Health and Human Services, Evaluation of Milk Laboratories**, 1995 edition.
12. M-A-85.
13. **Guide to Inspections of Dairy Product Manufacturers**, FDA, Office of Regional Operations, DFI, April 1995.

B. **ATTACHMENTS**

Attachment A -Sample Collection Form/Laboratory Results Report Form for use by the States.

Attachment B -Initial Drug Residue Report/Laboratory Results Report.

Attachment C -Report of Investigation Due to Positive Laboratory Results for Drug Residues Form.

Attachment D -Test Kit Problem Form.

Attachment E -Form letter for advising States of certain laboratory findings.

Attachment F -FDA Denver Laboratory, State Request for Special Sample Analysis

C. **PROGRAM CONTACTS**

ORA:
George Salem
Division of Field Science, HFC-140
(301) 443-3007

Barbara A. Marcelletti
Division of Field Investigations, HFC-130
(301) 827-5635

Randal Arbaugh
Division of Federal-State Relations, HFC-150
(301) 827-2904, FAX (301) 443-2143

CVM:
Deborah Cera, Program Monitor/Guidance
Compliance Information Managment Team (HFV-235)
(301) 827-0181

Dr. Linda Tollefson
Director, Office of Surveillance and Compliance, HFV-200
(301) 594-1768

Dr. N. E. Alderson (Beltsville Laboratory contact)
Director, Office of Science, HFV-500
(301) 827-8013

CFSAN:
William M. Baczynskyj, Program Guidance/Monitor
Domestic Programs Branch, HFS-636
(202) 205-4771, FAX (202) 205-9670

Joe Smucker, Chief
Milk Safety Team, HFS-626
(202) 205-8178

Dr. Larry Maturin, HFH-450
Chief, Laboratory Quality Assurance Branch
(708) 728-4115, FAX (708) 728-4179

Manjeet Singh, Compliance Issues
Case Processing Branch, HFS-607
(202) 205-5191
DEN-DO:
Emma Singleton, Laboratory Director
Denver District Laboratory, HFR-SW260
(303) 236-3060

PART VII - CENTER RESPONSIBILITIES

- CVM and ORA will develop analytical methods for drug residue testing.
- CFSAN, CVM and ORA will coordinate the technology transfer of new analytical methods including screening tests.
- CFSAN, CVM and ORA, on samples exceeding the safe or tolerance levels or positive results from official PMO methods will coordinate through the RMS, implementation of the enforcement plan with the states.
- CFSAN will notify states of drug residue findings that are at or above the limit of detection of the method and below the tolerance or the safe level.
- CFSAN Laboratory Quality Assurance Branch will prepare quarterly and annual reports of the findings from the NDRMMP. These reports will be submitted on a timely basis to the Domestic Programs Branch, HFS-636. CFSAN, ORA and CVM will review these reports before release.
- CVM, CFSAN and ORA representatives jointly will evaluate and revise (if needed) the NDRMMP at the end of the fiscal year to incorporate gained operational knowledge. CFSAN/Division of Cooperative Programs will take the lead in coordinating these efforts.
- CVM will coordinate regulatory follow-up relating to use of drugs for lactating cows.
- CFSAN will coordinate regulatory follow-up of milk and milk products.

NDRMMP
Sample Collection Form/
Laboratory Results Report

SAMPLE ID#:

COLLECTION DATE:

TIME OF COLLECTION:

TEMPERATURE:

FACILITY NAME:

ADDRESS:

PHONE:

FAX:

SITE (WHERE SAMPLE OBTAINED):

ADDRESS:

WEIGHT OF PREVIOUS WEEKS MILK

(RECEIVED AT SITE):

DRIVERS (HAULERS) NAME:

TANKER ID (PERMIT#)

LOAD WEIGHT IN LBS:

PRODUCERS (ID) ON LOAD:

GRADE/ANTICIPATED USE OF MILK (LBS OF

EACH):

COLLECTOR:

(SIGNATURE/DATE)

LABORATORY RESULTS:

DATE OF ANALYSIS:

TIME OF ANALYSIS:

TEMPERATURE:

CERTIFIED LABORATORY NAME:

ADDRESS:

PHONE:

FDA #:

TEST KIT/PROCEDURE:

LOT #:

EXP. DATE:

POSITIVE CONTROL:

NEGATIVE CONTROL:

RESULT:

COMMENTS:

CERTIFIED ANALYST(S):

(SIGNATURE/DATE)

NOTE: THE ORIGINATING LABORATORY KEEPS THE ORIGINAL OF THIS FORM AND SENDS A COPY TO THE FDA/CFSAN, LABORATORY QUALITY ASSURANCE BRANCH, HFH-450, SUMMIT ARGO, IL. 60501-1399, PHONE 708-728-4120, FAX 708-728-4179. WHEN SUBMITTING SAMPLES TO FDA Denver LABORATORY, ENCLOSE A COPY OF THIS FORM FOR EACH SAMPLE.

NDRMMP
INITIAL DRUG RESIDUE REPORT
LABORATORY RESULTS REPORT

SAMPLE ID# FOR LOAD TESTING POSITIVE:

SITE:

RESULT OF ANALYSIS:

CONFIRMING LABORATORY:

CONFIRMATION ANALYTICAL METHOD:

DATE OF REVIEW:

PRODUCER SAMPLES ANALYZED FOR TRACEBACK (NAMES OR ID#)(RESULTS):

NAME / RESULT

NAME OF PRODUCER RESPONSIBLE:

ADDRESS:

TEST KIT/PROCEDURE:

LOT #:

EXP. DATE:

POSITIVE CONTROL:

NEGATIVE CONTROL:

RESULT:

State REGULATORY OFFICIAL CONTACTED:

WHO:

HOW (PHONE/FAX):

WHEN (DATE/TIME):

ACTION TAKEN (DISPOSITION OF THE LOAD):

REGULATORY ACTION TAKEN AGAINST THE PRODUCER:

FDA CONTACTED:

HOW (PHONE/FAX):

WHEN (DATE/TIME):

BY (PERSON MAKING CONTACT):

THIS REPORT SENT TO:

WHEN:

SIGNATURE(S):

(CERTIFIED ANALYST/DATE)

(REGULATORY OFFICIAL/DATE)

NOTE: THIS FORM SHOULD BE USED FOR THE ANALYSIS OF INDIVIDUAL PRODUCER SAMPLES COLLECTED WITH A LOAD THAT TESTED POSITIVE. IF NO SAMPLES WERE AVAILABLE THAT CONTRIBUTED TO THE POSITIVE LOAD, AND THEY ARE COLLECTED AND ANALYZED LATER, ATTACHMENT A (SAMPLE COLLECTION FORM/LABORATORY RESULTS REPORT) SHOULD BE COMPLETED FOR EACH, AS WELL AS THE APPLICABLE PARTS OF THIS FORM FOR THOSE FOUND POSITIVE. THE REGULATORY AGENCY SHOULD

KEEP THE ORIGINAL OF THIS FORM. A COMPLETED COPY OF THIS FORM SHOULD BE SENT TO: FDA/CFSAN, LABORATORY QUALITY ASSURANCE BRANCH, HFH-450, SUMMIT ARGO, IL. 60501-1399, PHONE 708-728-4120, FAX 708-728-4179.

NDRMMP
REPORT OF INVESTIGATION DUE
TO POSITIVE LABORATORY RESULTS
FOR DRUG RESIDUES

Laboratory ID# for:

positive bulk milk pickup tanker:

Violative milk producer:

Drug residue analysis result:

Name/Title Investigator/Inspector:

Agency:

Address:

City/St/Zip:

Telephone:

FDA Contact:

This follow-up was initiated because:

Name milk producer:

Address:

City/St/Zip

Is the suspect drug still present on the farm? [] Y [] N

Does producer acknowledge treating animal(s): [] Y [] N

Brand name of drug(s) Used to treat animal(s)

Where was the drug obtained?

Veterinarian

Cooperative/Fieldman

Mail order distributor:

Feed/Supply store:

Other:

Were label directions for drug use provided? [] Y [] N

followed? [] Y [] N

Was the drug extra-labeled? [] Y [] N

Was the drug compounded by a Veterinarian (not a commercial preparation?: [] Y [] N

Drug dosage form(s):

Injectable Intermammary Infusion
Bolus Feed Additive

Other:

Were all drug(s) at this facility:
available for inspection? [] Y [] N

properly labeled? [] Y [] N

properly stored? [] Y [] N

Has producer completed a drug
residue avoidance program? [] Y [] N

Briefly describe PMO penalties assessed against this producer:

How many drug residue violations has this producer been responsible for during the preceding 12 months?

Comments:

Test Kit Problems Sheet[1]

Date:

Lab:

FDA#:

==========

Test Kit:

Lot#:

Exp. Date:

Date of Test:

Time:

Temp:

Sample ID:

Collection Date:

Performance Information, Complete as necessary:

Standard:

Other:

+Control Point:

-Control Point:

Positive Control:

Negative Control:

Test Results:

Duplicate #1:

Duplicate #2:

Interpretation:

Other:

Sample tested in another laboratory: Yes No

Denver (FDA):

Other:

If yes, list date sent/tested and result:

Nature of Problem and/or Comments:

[1] **- Please report any problems or inconsistencies you experience in using any of the rapid test kits to CVM so that they may be addressed.**

Dear

In cooperation with the National Conference on Interstate Milk Shipments (NCIMS), we are analyzing raw milk under the National Drug Residue Milk Monitoring Program (NDRMMP) Compliance Program 7303.039 for possible drug residues. FDA's Milk Safety Program relies heavily on participation by State regulatory agencies under a Memorandum of Understanding between FDA and the NCIMS. The NDRMMP is intended to assist and supplement the NCIMS program.

In addition to reporting drug residues above tolerance or the safe level to appropriate authorities, where possible we also intend to report to you the result of analyses for samples containing drug residues below the tolerance or the safe level. We intend to work with appropriate State and/or local authorities if any follow-up is needed.

Milk samples that are determined to contain drug residues above tolerance or safe level will be confirmed by further chemical analysis and reported to appropriate authorities for action as outlined in Parts IV and V of the program. Milk samples that are determined to contain drug residues below the tolerance or safe level will not undergo further confirmatory analysis.

In this context, sample_____, a (grade A/non-grade A) sample, collected by the _____ of _____ on _____ was found to contain _____ of _____. This finding is (above/below) the FDA tolerance/safe level of _____ for _____. We are reporting this to you for your information and follow-up that is appropriate following the provisions of your State Action Plan.

We appreciate the cooperation of all parties involved in this program.

If you have any questions or comments, or you need the assistance of FDA in this matter, please contact me at (202) 205-8178.

Sincerely yours,

Team Leader, Milk
Safety Team
Center for Food
Safety and Applied
Nutrition

FDA DENVER LABORATORY
STATE REQUEST FOR SPECIAL SAMPLE ANALYSIS

Requestor's Name, **Title** **State, Agency Address**	**Alternate Contact Person**
Phone Number:	
Fax Number:	
FDA Milk Specialist: Date/Time Notified:	
Sample Description:	
Firm/Producer/Location:	
Sample collection date/storage conditions:	
Purpose of sampling/analysis, i.e. referral, suspect contamination, adverse health affects, misuse, etc.	
SPECIFIC test requested, specific drugs:	
Collaborative information concerning sample, producer and animal(s). What other tests have been performed? State/Private Results?	

NOTE: CALL EMMA SINGLETON (301) 236-3060 TO REQUEST ANALYSIS. WHEN SUBMITTING SAMPLES, ENCLOSE A COPY OF THIS FORM FOR EACH SAMPLE. A COMPLETED COPY OF THIS FORM SHOULD ALSO BE SENT TO THE FDA REGIONAL MILK SPECIALIST AND TO FDA/CFSAN, LABORATORY QUALITY ASSURANCE BRANCH, HFH-450, SUMMIT ARGO, IL. 60501-1399, PHONE (708) 728-4120, FAX (708) 728-4179.