codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Via delle Terme di Caracalla 00100 Rome Tel.: 39.06.57051 Telex: 625825-625853 FAO I E-mail Codex@fao.org Facsimile:39.06.5705.4593

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

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CONTROL OF VETERINARY DRUG RESIDUES IN MILK AND MILK PRODUCTS

Governments and international organizations wishing to submit comments on the following subject matter are invited to do so **no later than 1 October 2001** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th and Independence Avenue, S.W., Washington, DC 20250, USA (Fax No.: +1.202.720.3157; e-mail: uscodex@usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org).

BACKGROUND

1. The 12th Session (March 2000) of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) considered a document presented by the United States concerning the control of veterinary drug residues in milk and milk products, which had been prepared in the format of an Appendix to the *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* (CAC/GL 16-1993).

2. The 12th CCRVDF agreed that the United States would redraft the paper, taking into account written comments and the Committee's discussions, for circulation, comment and consideration at the 13th CCRVDF. The Committee also agreed to consider whether on not to initiate work on additional appendices to address the control of veterinary drugs in other specific groups of animal products, including honey, at its current meeting (ALINORM 01/31, paras. 121-125).

3. As directed above, governments and international organizations are invited to comment on the attached proposed draft Appendix to the Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods, which concerns the prevention and control of drug residues in milk and milk products.

PREVENTION AND CONTROL OF DRUG RESIDUES IN MILK AND MILK PRODUCTS

1. Objective

To present elements for consideration in the design of programs for the monitoring of drug residues in raw milk of dairy animals

2. Introduction

2.1 Need for Milk Monitoring

The misuse and the abuse of drugs in the treatment of lactating dairy animals can result in the contamination of milk with levels of drug residues in excess of established Maximum Residue Limits (MRL's) thereby rendering the milk unsuitable for human consumption and for food product manufacturing. In addition to being a human food, milk is also a component that is often used in the manufacture of other human food products. This provides multiple paths for drug residues to occur in other human food products. The overall strategy for the prevention of drug residues in milk and related food products is based on procedures and drug use at the farm level.

2.2 Focus for Milk Residue Control

A typical event that leads to the contamination of milk with drug residues exceeding the MRL, is the failure to withhold the milk for a time sufficient to allow drug residues in the milk to deplete below the MRL. The decisions associated with the administration of drugs to lactating dairy animals that results in the contamination of milk with drug residues, occurs at the farm level. Since the goal of a milk residue avoidance program is to prevent contamination of milk with illegal, violative residues, prevention control practices must be employed at the farm level. Thus, effective residue prevention control programs are characterized by management practices that will promote healthy animals and disease prevention and assure prescribed use of any animal drug.

3. Prevention of Drug Residues in Milk

3.1 Responsibilities of the Milk Producer and Veterinarian

The prevention of drug residues in the milk supply is the responsibility of the dairy industry and the regulatory authorities. This responsibility rests primarily on the dairy producer, who controls the hygienic conditions of the milk production facility and the environment of the dairy animals and administers drugs to dairy animals. The dairy veterinarian who controls the selection, administration and the use conditions of drugs administered to dairy animals shares this responsibility.

The veterinarian should also ensure that the use of a drug in dairy practice meets the standards of good veterinary practices. Both the milk producer and the veterinarian share the responsibility to strive to limit drug use to the minimum necessary regimen.

The cooperation and commitment of the milk producer and the veterinarian are critical to the success of any residue control program. A prevention program requires proper management of animal health and drug use by the dairy producer and veterinarian at the farm level. This program may involve the application of disease prevention measures such as the separation of treated animals from the rest of the production herd, physical marking of the treated animal, record keeping, utilizing separate milking equipment or milking treated animals last. Compliance with drug label directions and screening of the milk from treated animals prior to commingling with the rest of the milking herd are very important prevention practices.

3.2 Responsibilities of the Milk Industry

The responsibility also rests on industry quality control personnel who are responsible for educating dairy producers in proper milk handling practices and screening raw milk for drug residues. That responsibility extends to the processing plant quality control personnel who make the final evaluation and screening of the raw milk prior to processing. After the milk has left the farm for processing, industry is responsible for monitoring or screening programs to determine if the commingled raw milk is free of unacceptable drug residues.

3.3 Responsibilities of Government Authorities

The regulatory agency/government's role is to verify that the prevention systems established by the dairy industry to comply with government/regulatory requirements are adequate, valid and effective in maintaining a safe milk supply. Effective control of drug residues also includes regulatory measures such as the licensing of drugs and the provision of the acceptable condition of use. Also, regulatory authorities must establish adequate sanctions and enforcement procedures to ensure that milk remains in compliance with MRL requirements. Lastly, all parties responsible for the maintenance of a milk supply compliant with MRLs should periodically critique their residue control procedures to assure continued adequate performance.

Government/regulatory agency efforts at auditing or verifying the industry program may include screening of commingled milk at the farm level, screening of commingled milk at the transport tanker level and testing of finished dairy products for drug residues.

A successful program requires all parties to establish an acceptable prevention and monitoring program and to carry out their part of the program to attain a milk supply free of hazardous drug residues.

3.4 Audit of Dairy Farm Management and role of HACCP

The development of a practical and effective residue prevention program at the dairy production level should begin by identifying those herd management practices which may contribute to the occurrence of violative drug residues. This involves a review of herd management procedures and other milk production techniques for the purpose of identifying critical points in the milk production process where controls and intervention practices are essential to minimize violative drug residues in milk In reality this strategy is the application of the concepts of prevention and control, associated with the Hazard Analysis Critical Control Points (HACCP) process. The information derived from a HAACP analysis of milk production operations can be very helpful in developing an effective and efficient drug residue control strategy for milk.

3.5 Principal Characteristics of Milk Residue Control

There is no single drug residue prevention program that can be utilized for all dairy farms. Dairy farms vary in size, location, environmental conditions, economics and level of management skills. Specific techniques will vary to meet the specific needs of the dairy farm. To be effective, residue prevention programs need to be practical and effective for the individual dairy producer responsible for the prevention of drug residues in milk produced on the dairy farm.

However, regardless of the size of the farm or other variable management practices, it is important that veterinarians and milk producers use drugs according to the approved labeled specifications and observe proper withdrawal times for the drug used. These two specifications are critical elements in every residue prevention control program. Specific consideration should be given to these critical elements as well as the general standards of good veterinary practice.

The first step in preventing the occurrence of drug residues in milk is to maintain a healthy herd and employ herd health practices that will minimize the need to use animal drugs. Proper management of the animal's environment by the dairy producer can improve the health of the dairy cow and thereby lower the frequency and

amount of drug use on the dairy farm. Maintaining hygienic practices that assure cleanliness of the milk production facility and a clean cow environment can have a major impact in preventing the development of disease in the herd thereby minimizing the need drug use.

Animal drugs and syringes used for drug administration should be located and stored in an area that will exclude accidental contamination of milk, the storage vessel and the milking equipment with drugs or drug residues. In addition, all drugs should be labeled with information pertinent to the proper and safe use of the drug. This information should include the identity of the drug, including any batch or production numbers, the directions for use including milk withholding times, any special precautions, storage conditions, shelf life and the names and addresses of the manufacturer. In the event the drug is used in an extra-label manner, the name and address of the prescribing veterinarian should appear prominently on the label.

Because the information on the label of the drug is designed to prevent the occurrence of violative drug residues in milk, milk producers should follow the labeled instructions carefully and keep accurate records of the use of drugs on each treated dairy animal. These records should capture such information as the date, time, identity, dosage, and route of administration of the drug and appropriate milk withholding times. In the case where the drug is used in a manner different for what is prescribed on the label, the name and address of the veterinarian who prescribed it, as well as the conditions of use, should appear separately on the label or on the prescription.

In addition, all treated animals should be physically identified and isolated if practical. To assure that milk from treated animals is not accidentally commingled with milk offered for sale, separate equipment must be used to collect this milk or these treated animals should be milked last after the equipment has been isolated from the milk storage vessel. The milk should be discarded or diverted to other recognized uses that have been approved to protect the human food chain. Milk from treated animals may be offered for sale if the withdrawal time as well as other labeled instructions have been followed.

4. Monitoring for Drug Residues in Milk

The prevention of violative drug residues in milk is a proactive undertaking which deals with animal drug use practices. Prevention of conditions that may result in residues in milk above the MRL, is always the best and most cost effective public health policy.

4.1 Function of Residue Monitoring

Residue monitoring programs are intended to detect the occurrence of violative residues in milk prior to processing and sale to the consumer. These programs can involve the screening of raw commingled milk at the farm or during transport the control of the diversion and disposal of milk found to contain drug residues and an investigation to determine the cause of the residue. Remedial actions can be educational in nature to promote and encourage proper use of animal drugs or involve legal action by regulatory authorities against the individual causing the residue.

It is important to keep in mind that residue detection programs are not intrinsically designed to prevent or remediate residue contamination problems. Monitoring programs can identify the existence of a violative residue and thereby indicate milk that should not be consumed or be used for the production and processing in a human food product. Monitoring programs, regardless of the degree of sophistication of the analytical methods used, cannot prevent the occurrence of animal drug residues in milk.

4.2 Factors Affecting Milk Residue Monitoring

The procedures used in the collection and manufacture of milk usually involves the commingling of milk from individual animals. In practice, this means the milk intended for human consumption originates at the farm bulk tank and not directly from individual animals. Monitoring of residues in the farm bulk milk holding tank offers the practical advantages of clear identification of the farm that caused a drug residue and will allow effective remedial or regulatory action by authorities. Testing of the farm bulk tank milk is analogous to the testing of raw material for acceptance for use in further manufacturing.

Rapid test kits for milk residues have been developed for use on raw bulk tank milk. Milk added to the bulk tank should come from animals that are healthy or if the animal has been under treatment, that the animal has been judged healthy by a veterinarian for milking purposes. This allows for a relatively consistent milk matrix for use with the test kits thereby permitting good analytical performance. Most test kits have been developed and validated using bulk raw milk. More sophisticated chemical methods could be used to test individual animal milk that would obviate the matrix variability, but these tests would likely take a longer time to perform and require shipping of a milk sample to a laboratory. Since milk has a limited shelf life, the use of these sophisticated chemical tests for manufacturing acceptance decisions could be an impediment to the provision of a wholesome product to consumers. However, if regulatory authorities are considering legal action in a milk residue monitoring situation, the use of sophisticated chemical methods may be necessary.

Although dilution of milk is an inherent part of the collection and processing of milk, the dilution effect during the processing of milk does have a negative impact in the analytical testing aspects of residue monitoring. For example, if the raw milk collected at the dairy farm is diluted by a factor of 100 when the farm milk is added to the milk holding tank at the milk processing facility, then the occurrence of a residue of ampicillin of 100 micrograms/Kg in the farm bulk tank would ultimately result in a fluid milk product of 1 microgram/Kg. Even if the bulk tank residue were not detected, the manufacturing process would result in a product that contained residues below the MRL for ampicillin.

Dilution of raw milk is common practice in the manufacturing of fluid milk for human consumption. While the dilution of raw milk collected at the farm can result in a reduction of the concentration of drug residues in fluid milk for human consumption, dilution also results in a progressively more difficult drug residue monitoring problem. Analytical methods exist that can detect ampicillin in the bulk tank at 100 micrograms/Kg down to 5-10 micrograms/Kg. The limit of detection of the methods available for ampicillin provides a high probability that violative residues in the milk in the above example would be detected. However, after further dilution of the milk in the milk processing facilities holding tank, the probability of detecting residues is significantly reduced.

This practical example draws attention to the fact that while drug residue analytical monitoring programs can provide many advantages in detecting and correcting drug residue occurrences, the analytical methods also have limitations wherein drug residue contamination of milk could escape detection and remediation.

This limitation of analytical methods emphasize the fact that the first priority for an effective program for the control of drug residues in milk must be for proper and necessary drug use at the dairy farm.

4.3 The Effect of Milk Processing

There is also the question of the effect of processing on the concentration of drug residues in milk. Unfortunately, the scientific literature for the effects of processing on drug residues in milk is insufficient to permit clear determination of the effect, if any, that processing may have on the level of most drug residues that could occur in milk. Available literature suggests that reconstituted milk from spray dried powder is not different from raw whole milk with respect to the concentration of procaine penicillin and sulfamethazine. There was no loss in the activity of these antibiotics in either the raw milk or in the spray dried milk that was made from the raw milk. Additional studies are needed in this area.

Research on the effects of cooking temperatures on the stability of various antimicrobial drugs indicates that there is variability in the stability exhibited depending on the antimicrobial tested. While most antimicrobials ultimately demonstrated reduction in potency when subjected to cooking conditions, the temperature conditions under which these stability studies were performed, e.g. 100-260 degrees Celsius were generally more severe that heat conditions use in milk processing.

While this data does not provide scientific information for the stability of drug residues in milk during milk processing, the data does provide for speculative consideration that it is possible for drug residues in milk to survive processing conditions.

The distribution of drugs between polar and non-polar constituents of milk appears to be a function of the concentration and route of administration of the drug as well as the polar characteristics of the drug. Experiments with benzylpenicillin, spiramycin, chloramphenicol, dihydrostreptomycin and tetracycline indicate that in general, intramuscular use of these drugs tends to increase the amount of drug in both the cream fraction and the casein fraction of whole milk. Intramammary use of the same drugs results in a different distribution of the drugs in commingled milk.

The effects of the pharmacokinetics and the physical chemistry of drugs used in dairy cattle can determine the distribution of the drugs between milk components. This should be considered in the establishment of control points in a milk residue prevention/control program and in the design of validation studies for the certification of analytical methods for residue monitoring. Ideally, the metabolism and pharmacokinetics of an animal drug in dairy cattle should be determined to permit manufacturing procedures to be rationally developed to prevent or minimize the probability of occurrence of drug residues in milk. Furthermore, the design of validation studies for screening tests for drug residues in milk depends on knowledge of the distribution of drugs in milk. Any effects of protein binding or lipid association that may make a drug residue more difficult to detect must be known and resolved.

4.4 Data Needed for Monitoring Method Development

Metabolism and pharmacokinetic information on drug residues in dairy cattle is the scientifically preferred way of achieving critical initial information relative to the occurrence of drug residues in milk for screening method development and validation. While this information is generally available for newer dairy drugs, this information, especially metabolism information, may not be readily available for older dairy drugs. Where metabolic information is not available, an alternative, indirect strategy can be considered for validation of the screening methods that may be needed for monitoring.

4.5 Screening Method Validation

Since it is preferred to know the concentration of the drug residue in milk, an alternative strategy would use a chemical reference method that has been validated to extract and measure all of the parent drug (or other marker residue, if known) that may be present in the milk. Reference methods for the marker residue for approved dairy drugs are usually contained in the data dossiers used for the evaluation and establishment of the MRL. Regulatory authorities can be requested to provide these reference methods for use if they are available.

Control milk that has been fortified at appropriate levels with the drug of interest is prepared. Lactating dairy cattle are then administered the drug through an appropriate route and milk containing residues of the drug is collected. This milk is called “incurred milk”. All milk, both fortified and incurred milk, is assayed for the drug residue content by the chemical reference method. The residue values assayed by the screening test(s) are compared to the reference method values. Screening test values significantly less than the reference values could mean that the entire drug residue in milk containing incurred residues, is not available to the screening test for measurement. In such a case a more detailed investigation of the validity of the screening test is required prior to initiation of a monitoring program using the screening test.

This procedure is an approach to determining whether a screening test is capable of providing acceptable results on the presence of a drug residue in raw milk. This procedure does not establish the MRL or other residue safety limit. Data requirements for the establishment of MRLs are specified by JECFA. Where dairy drugs are in use that have no MRL, or are used in an extra-label manner, the estimation of a food safety monitoring level may be possible through the use of available relevant scientific data such as toxicological information concerning the drug or drugs of the same class, use of the drug, etc. This information could be useful in a risk analysis of the human food safety for expected residues of the drug in milk. This should be considered an interim approach only, with the goal of pursuing a full determination of an MRL for the drug.

This alternative strategy has been successfully used for the evaluation of screening tests for beta-lactams. In this evaluation, the screening test results satisfactorily agreed with the reference method, thereby indicating the suitability of the screening tests for initial residue monitoring of these drugs at specified monitoring levels.

An operational program should be implemented so that appropriate analytical procedures, to the extent possible, take the above factors into consideration. Screening tests, if employed, should agree with the reference method, thereby indicating the suitability of the initial screening test for residue monitoring. Of course, full regulatory enforcement of established maximum residue limits (MRL) requires that the initial screening test result be confirmed by an analytical method that has been validated as suitable for regulatory confirmation at the MRL.

4.6 Necessity for Screening Test Confirmation

The need for confirmation of screening test results prior to initiation of regulatory action cannot be overemphasized. Many screening tests do not give an analytical response at one unique drug concentration level rather they give a positive responses over a range of drug concentration values. This characteristic of some screening tests is not a deficiency or malfunction of the test but results from way in which the screening test has been technically developed. This results in a situation where a screening test positive result may be a true analytical positive but a false violative result with respect to the MRL. A confirmation procedure can determine whether a screening test positive result is an actual violative result.

There is no single scientific strategy for confirming analytical results. The configuration of a confirmatory procedure depends on the intended use of the confirmatory data. Government regulatory authorities generally require both quantitative information and data that will allow identification of the drug or chemical residue in milk since this information is typically used to enforce laws or other regulations. In all cases, however it is essential that the confirmatory procedure be validated, i.e. demonstrated to be fit for the intended use. Government regulatory authorities may require that the validation of confirmatory methods demonstrate that the method meets internationally recognized and accepted performance criteria.

Verification of the initial screening test results by repeating the test using additional positive and negative control can also provide useful residue information. Verification of the initial test results can provide greater confidence in the residue statue of the milk. This is based on the premise that the function of a screening test is to give a highly reliable indication when the milk may contain drug residues above the MRL. A positive screening test result indicates the presence of a drug residue and that further investigation or action is warranted. Stated in another way, a negative result with a properly validated screening test means that no further testing is necessary for drug residues that are capable of being detected by the screening test.

4.7 Positioning of Screening Tests in a Residue Monitoring Program

A drug monitoring program, using analytical screening methods that have been validated and are routinely available, should be undertaken at an early point in the processing of raw commingled milk. From a practical standpoint, sampling at the dairy farm or the milk transport tanker level has proven effective. This allows intervention and trace back to the farm to occur, prior to the use of the milk in the manufacture of milk based products.

It is preferable that screening tests applicable, to the extent possible, for the spectrum of drugs used in animal disease prevention be used in combination with appropriate confirmatory tests. The AOAC International Research Institute has validated commercially available rapid screening methods for milk residues, primarily beta-lactams. The availability of rapid screening methods for milk residues allows monitoring programs to systematically test large numbers of raw commingled milk samples for residues, thereby decreasing the probability that milk containing violative residues would be used to manufacture milk based products.

This strategy prevents unnecessary delays that can result in the loss of safe and wholesome milk. It is also an expeditious and economic means to assure the safety, wholesomeness and regulatory acceptance of raw commingled milk, and gives the best certainty that violative drug residues will not be introduced into the human food manufacturing process.

If screening tests are used at the milk processing plant, the testing for residues should be done prior to the processing of the raw fluid milk. This allows intervention to occur prior to the use of the milk in the manufacture of milk and milk-based products. Focusing at this level will also reduce the volume of contaminated commingled raw milk, the potential contamination of processing equipment and finished dairy products. This strategy also prevents unnecessary delays that can result in the loss of a safe and wholesome milk supply. Furthermore, testing of the raw commingled milk for drug residues offers an economy of scale that provides for maximum cost efficiency.

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