Current Issues and Topics Concerning the Bovine Practitioner

Stephen F. Sundlof, *DVM, PhD*
Director, Center for Veterinary Medicine
FDA HFV 1, Metro Park
Rockville, MD 20855

As regulators under the Food, Drug, and Cosmetic Act, our first concern is always to protect the public health; our second concern is to ensure the safety, efficacy, and availability of the animal drug supply. The best way to ensure both objectives is to design cooperative and efficient processes that encourage sponsors to collect good data on the safety and efficacy of their animal drugs and to seek FDA approval to market them.

CVM Strategic Plan

When CVM came under new management in 1994, there was an immediate effort to analyze the organization as to needed improvements. It was determined that the Center was operating effectively when measured in the "old paradigm," which focused on protecting human health and safeguarding the public from fraud. These are still important. However, equally important is assuring adequate availability of animal drugs. Over the last year, the Center has been engaged in developing a five- year strategic plan to determine where the Center should be and to map a course for the Center to follow to get us there. The Center's Strategic Plan is the mechanism by which we intend to change how we do business.

I won't go into an explanation of the plan now, but let me tell you a little of our thinking. We have set five goals for ourselves. For our purposes today, I especially want to read our first goal to you. **"We will re-engineer product evaluation, surveillance and compliance, research, and administrative processes to increase the availability and diversity of safe and effective products."** Under each of these goals are numerous strategies, objectives, tasks and elements describing how we will accomplish this goal. Individuals throughout the Center are involved as members of Strategic Implementation Groups charged with completing the various objectives to enable the Center to reach its goal.

Our thinking relating to this first goal is that drug availability needs more emphasis because a lack of available drugs adversely affects food safety. When unapproved drugs are used or when approved drugs are used under conditions other than specified on the label in treating food-producing animals, the safety of animal-derived food is potentially compromised. By ensuring the availability of animal drugs that are manufactured to specific standards of quality, purity and strength and are demonstrated to be safe and effective, the safety of animal-derived food is better ensured.

Another goal I'd like to mention here today is our fifth goal and that is **"We will employ effective communications as a vital means of sharing information within CVM and with our customers."** AABP is one of several organizations that have actively participated in discussions with the Center on a variety of issues of mutual concern. We look forward to sustaining and enhancing these very professional communication opportunities.

There are three other goals dealing with work force development, teamwork and resources. The strategic plan is our road map. We have strategies and objectives in place to help us realize these goals before the year 2000. You will be hearing more about these activities and possibly be involved in some of them over the next few years.

Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA)

I would like to take a few minutes to talk about some of the recent legislative activity that concerns you as bovine practitioners. Some of you may be wondering why CVM is so concerned about drug availability given that the law prohibiting extra-label use was modified when Congress passed the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA). I would like to describe for you what the law provides and what it does not. First, let me start by saying that the passage of this Act brought to a successful conclusion several years of diligent efforts by the American Veterinary

Medical Association (AVMA) and other organizations to legitimize extra-label use of approved drugs in animal medicine.

AMDUCA specifically authorizes the extra-label use in animals of *approved* animal and human drugs. That is, the new law permits use beyond the labeled conditions of use for an approved animal drug, and use of an approved human drug in animals. There are two important general limitations, however. The drug must be used within the context of a veterinarian/client/patient relationship, and the use must be in compliance with FDA regulations that establish the conditions for extra-label use. Another significant limitation is that the law does not permit extra-label use of drugs that are administered through animal feed.

It is important to note that the law will not go into effect until FDA adopts the attendant regulations. Congress gave the Agency two years to do so, that is, until October 1996. Until the regulations are final, FDA will continue its compliance policy guides, which I will describe in a few minutes.

The major purpose of the law is to decriminalize the every day practice of veterinary medicine by allowing veterinarians to meet legitimate practice needs and, at the same time, provide FDA with tools needed to assure continued safety of the food supply in the presence of extra-label use of drugs in food-producing animals.

Among other provisions, AMDUCA gives FDA authority to prohibit specified extra-label uses. Thus the regulatory scheme does continue to differ from that in human medicine, in that Congress — which has never imposed a general prohibition on extra-label uses by human practitioners — has not given FDA explicit authority to prohibit specific extra-label uses in human medicine.

While the new law does permit use beyond the labeled conditions of use of *approved* drugs, the legislation is not intended to address the problem of insufficient drug approvals. New legislation has been introduced in Congress this year to deal with animal drug availability issues.

It is important to note that AMDUCA is intended generally to codify current FDA discretionary practice. FDA has, for more than a decade, regulated extra-label use of approved animal drugs under the parameters of Compliance Policy Guide 7125.06. That guide identifies limited circumstances under which CVM will not ordinarily object to extra-label use in *food-producing* animals. The guide states that FDA will not usually object to extra-label uses of approved animal drugs in <u>non-</u>*food-producing* animals.

The CPG states that FDA will not ordinarily consider enforcement action in the case of an extra-label use in food animals "when the health of animals is immediately threatened and suffering or death would result from failure to treat the animals," and when several criteria are met.

As in the case of animal drugs, pre-AMDUCA law did not permit use of human drugs in animals. Again, FDA has in the past exercised enforcement discretion in certain instances, under CPG 7125.06. The CPG emphasizes that use of human drugs in animal medicine is to be a practitioner-driven practice, that is, it discourages promotion of human drugs for animal use by manufacturers and distributors. The CPG also limits use of human drugs in animals mainly, but not exclusively, to nonfood- producing animals.

The new law establishes certain procedures for FDA to follow in regulating extra-label uses. A stepwise procedure applicable primarily to use in food animals allows FDA to establish standards, and impose requirements or obtain information based on public health concern related to extra-label uses. If FDA finds that there is a *reasonable probability* that an extra-label use *may* present a risk, the Agency can:

a. Establish a safe residue level for an extra-label use, e.g. in a species for which the drug is not approved. Any amount of residue resulting from an extra-label use constitutes a violation of the Food, Drug, and Cosmetic Act if a safe level has not been established. Notice and comment rulemaking, or formal rulemaking, are not required for the establishment of a safe level.
b. Require development of an assay method for detecting the residue. FDA can call for the development of an analytical method related to a specific extra-label use but cannot impose a requirement on a sponsor to develop a method.

If the FDA finds that an extra-label use *may present a risk* to the public health, the agency can gain access to veterinarians' records to obtain information about the extra-label use. If the FDA finds that an extra-label use *presents a risk,* or a *required method is not developed*, the Agency may after public notice *prohibit* the extra-label use. Notice and comment rulemaking is not required as a prerequisite to prohibiting an extra-label use. Extra-label uses that FDA has prohibited through its existing CPG can be prohibited under the implementing regulation without following the public notice procedure under the new law.

The procedure is stepwise but not lock step, i.e., the Agency does not have to go through all the steps listed to prohibit a drug, as long as the Agency finds that an extra-label use presents a risk, or the required method is not developed.

It should be clear from the nature of these procedural steps that this portion of the law is intended primarily for use of drugs in food-producing animals.

Withdrawal of the underlying approval, on the basis of extra-label use, remains an option to the Agency but only through the withdrawal procedures contained in section 512(e).

AMDUCA specifically authorizes use of human drugs in animals provided that there is a VCPR and the use is in accordance with FDA regulations. The law provides no additional detail.

As we prepare to write the implementing regulations, we have sought the advice of CVM's Veterinary Medicine Advisory Committee. VMAC consists of 11 highly qualified experts representing scientific disciplines, professional practice and species groups. The committee, as well as members of the public, gave CVM advice on a variety of AMDUCA - related extra-label use topics during a meeting held in May 1995.

Here are some highlights from the committee discussions. We asked the committee questions on the following topics among others:

1. *What scientific data should be provided in order to establish safe levels for residues?* Most of the discussion centered around the comparative metabolism data required for extrapolation from approved to non-approved species. The committee generally urged caution in making such extrapolations.
2. *What extra-label use information should be made available to practitioners?* Much of the discussion here centered on the idea of setting up a clearinghouse for such information. Committee members expressed concern about the volume of material that would need to be reviewed.
3. *Should extra-label use be permitted for other than therapeutic treatment of animals?* The discussion centered around use for reproductive purposes such as sex reversal in fish. In general, committee members favored extra-label use for reproductive purposes, although several suggested limits on such use.
4. *Should extra-label use be permitted for fluoroquinolones in food-producing animals and in non-food producing animals?* Those committee members who responded to the questions generally expressed the view that extra-label use of this class of drugs could be permitted in nonfood-producing animals, and in food-producing animals with certain limitations (e.g., include minimal dose and/or maximum length of administration).

Comments from the committee, and the public, will be considered as we draft the regulations.

The extra-label use legislation creates a substantial challenge for veterinarians as well as for CVM's pharmacovigilance program. We expect more adverse drug reaction reports from uses for which few or no data on safety or effectiveness are available. Additionally, there is a poor track record for the human drug sponsors in reporting ADRs in animals associated with human products. There are presently no reports of ADRs in animals treated with human products from a human product sponsor in our 8000-report inventory. The point I wanted to make is that while AMDUCA solved one problem, it may have created others.

Given the limitations and the potential adverse drug problems, we believe that the passage of AMDUCA supports the need to have more veterinary products available which have met the rigors of the approval process. Rather than deregulating, we believe the answer to drug availability lies with reducing the need for extra-label drug use by increasing the flexibility of our pre-approval data requirements and by expanding labeling.

I want to briefly mention that Senator Kassebaum has introduced a bill known as the Animal Drug Availability Act of 1995. The intent of the bill is to enhance the review of new animal drug applications by CVM and to amend the Food, Drug, and Cosmetic Act toward encouraging animal drug availability. FDA, including CVM, has not taken a position on the bill at this time. I want to mention it here today to let you know that there is legislation underway to balance animal drug needs with availability in light of passage of AMDUCA.

Extra-Lable Use of Fluoroquinolones in Food-Producing Animals

On August 18, 1995, the Food and Drug Administration approved a new fluoroquinolone antibacterial, sarafloxacin, for use in chickens and turkeys. Sarafloxacin is the first fluoroquinolone approved for use in food-producing animals. It is a prescription drug distributed under the trade name Saraflox WSP® by Abbott Laboratories, North Chicago, Illinois. Saraflox WSP® is indicated for administration in drinking water for use in broiler chickens and growing turkeys for the control of mortality associated with *Escherichia coli* organisms susceptible to sarafloxacin.

Fluoroquinolones are the newest class of antibiotics developed for treating infections in humans and animals. On May 11 and 12, 1994, CVM's Veterinary Medicine and the Center for Drug Evaluation and Research's Division of Anti-Infective Drugs Advisory Committee heard presentations from human and animal health researchers and producers relative to questions raised about the development of bacterial resistance to fluoroquinolones. Members of both committees concluded that FDA could approve fluoroquinolones found to be safe and effective for animal use.

CVM is interested in preserving the usefulness of

this valuable new drug and other fluoroquinolones by minimizing the potential for development of resistant pathogens. In order to achieve this objective CVM believes it will be necessary to minimize unnecessary treatment of animals that may increase the potential for developing fluoroquinolone resistant pathogens. To facilitate accomplishment of this important objective, CVM is initiating an educational program to inform veterinarians and producers about the appropriate use of fluoroquinolones and is revising the Compliance Policy Guide 7125.06, Extra-Label Use of Animal Drugs in Food-Producing Animals to include regulatory guidance for fluoroquinolones. A recently issued CVM Update provides a synopsis of the proposed regulatory guidance.

The regulatory priority that FDA will assign relative to control of the extra-label use of this class of drugs will depend on its actual use. The highest priority will be for extra-label use of fluoroquinolones in major food-producing animal species and classes of species that are not covered by the approved labeling. A lesser regulatory priority would apply to extra-label use of fluoroquinolones in minor food-producing species or within a major food-producing species or class for which the drug is approved but for which the actual use is not included in the approved labeling of the drug.

FDA is collaborating with the U.S. Department of Agriculture and the Centers for Disease Control and Prevention (CDC) to develop a surveillance system to monitor antimicrobial resistance in enteric pathogens. Under the program, USDA periodically will test *Salmonella* samples from animals for continued susceptibility to antimicrobial drug products. CDC will conduct similar testing on samples of human *Salmonella* and *E. coli.* The manufacturer will test samples of animal *E. coli* to measure the emergence of any resistance in the drug's target organism. Abbott Laboratories will also provide geographically based drug distribution information to CVM as part of their annual Drug Experience Reports. The information from the monitoring programs will be used to assess the development of antibiotic resistant organisms and make any adjustments in the regulatory program.

Please feel free to direct any questions regarding CVM's position on the extra-label drug use of fluoroquinolones to CVM at (301) 594-1761.

Veterinary Feed Orders

A broad coalition representing veterinary organizations, the feed industry, animal drug industry, producer groups and others joined together in recent months to propose a "veterinary feed order" system. The VFO concept is intended to provide an alternative to "prescription" status under the Food, Drug, and Cosmetic Act. The concept would apply when FDA concludes that it is unable to approve a new antimicrobial drug for use in feed, in the absence of greater controls over its use than the over-the-counter system provides. Industry groups objected to approval of feed use drugs under current prescription law because, among other reasons, prescription feeds could trigger state pharmacy laws, which we intended to apply to dispensing of dosage form drugs.

The legends on the type A articles and type B and C medicated feeds would be different than the prescription legend. Feed mills and downstream distributors would be allowed to handle and dispense these articles, but the medicated feed could not be dispensed to producers until a veterinarian issued a VFO in the course of his or her professional practice.

FDA's Office of General Counsel has reviewed the proposed VFO scenario and has tentatively concluded that the proposed system cannot be implemented under current law. The law establishes the prescription system for regulation of drugs that require a veterinarian's intervention, and any such drugs need to be regulated under that provision. The Center for Veterinary Medicine and industry groups are exploring alternatives, including legislative changes, and discussions are continuing.

The coalition effort has been an unprecedented action bringing together an extremely broad range of stakeholders in an attempt to solve a problem. CVM appreciates and encourages such efforts. We view the VFO initiative as an opportunity for forging the kind of government/industry partnership that is part of reinventing government. We will continue our efforts to find a way to make the VFO concept a reality.

Flexible Labeling

The Center for Veterinary Medicine (CVM) recognizes that most approved drug labels provide limited information and restrict drug usage to specific fixed (point) doses for limited claims. Such label restrictions have contributed to the limited usefulness of many approved drugs. As a result, it is not surprising that veterinarians find themselves frequently using drugs in an extra-label manner and doing so with very little information, let alone quality information, to support their therapeutic decisions. Some of the current limitations associated with many drug labels include:

1. Fixed or point doses that do not allow any flexibility to select dose based on organism susceptibility or other clinical factors.
2. Drugs approved for use in a limited number of animal species for the treatment of limited claims and pathogens.
3. No information to predict clinical efficacy of drug based on the *in vitro* suscepetibility of the organism.
4. Withdrawal time information provided on the label is only valid for the single approved fixed dose.

Prescription veterinary labels have not provided therapies to particular situations. This is confounded by the limited availability of approved drugs to treat many diseases and/or animal species. Moreover, although the 1994 extra-label use legislation has relieved some of the pressure on the practitioner, liability for extra-label use is still present. In fact, a veterinarian may still have to defend the basis for an extra-label use in a civil liability suit. The frequent necessity for extra-label drug use is a symptom of the underlying problems of drug availability and restrictive drug labeling. We have perhaps alleviated the symptom but have not taken steps to cure the underlying problem. On a positive note, these concepts are currently part of the curriculum of many veterinary education programs and are likely to become commonly used concepts in veterinary practice, allowing us to move drug labeling to more closely reflect a veterinarian's expertise. The endeavor to utilize new types of information in the drug approval process to enhance drug labels and increase drug availability has been coined "Flexible Labeling."

CVM has been interested in the flexible labeling approach for a number of years. In 1991, the Animal Health Institute (AHI) and the American Veterinary Medical Association (AVMA) jointly filed a Citizen Petition requesting that the Center for Veterinary Medicine (CVM) consider alternative data to facilitate the drug approval process. The Citizen Petition represented the culmination of several years of work with the AVMA, AHI, and CVM. One concept proposed in the Citizen Petition was alternative data for drug approval including the use of pharmacokinetic (PK) and minimum inhibitory concentration (MIC) information to help satisfy efficacy requirements. As an extension of this concept, CVM has been working to develop ways to utilize such alternative data to not only facilitate drug approval but to enhance drug labels as well.

Currently, the flexible label exists only as a concept that has yet to be defined. CVM and several outside organizations are in the process of defining flexible labeling. To that end, CVM held an internal seminar in January 1995. In April 1995, the AAVPT, FDA/CVM, AHI, and AVMA sponsored a Professional Flexible Labeling Workshop. In May 1995, AHI and FDA co-sponsored a workshop on the Target Animal Safety issues related to flexible labeling. We look forward to another workshop to discuss flexible labeling issues in December 1995.

Some objectives of the flexible labeling approach include:

1. To enable veterinarians to select dose from an approved dose range.
2. To provide adequate information (e.g., pharmacokinetic/dynamic and MIC) to facilitate selection of appropriate dose.
3. To enable veterinarians to tailor dose so as to maximize the therapeutic benefit to the patient while minimizing the potential for development of bacterial resistance.
4. To reduce the necessity for extra-label drug use and to provide information that will enable the veterinarian to make informed decisions when extra-label use is necessary.
5. To provide expanded withdrawal time information to accommodate the extended dose range concept and reduce drug residue concerns.
6. To increase drug availability by facilitating the approval of drugs with multiple doses, species, routes of administration, disease indications, and withdrawal times.

The inclusion of additional information on drug labels, such as pharmacokinetic and MIC data, could greatly enhance the utility of the drug for the veterinarian. If prescription drug labels provided adequate and detailed information, the practitioner could have more flexibility to use his/her professional judgment to determine how and when to use the drug without resorting to extra-label use nearly as often.

NCIMS Monitoring

Over the past few years, we have become concerned about the reliability of screening tests being used to test milk for animal drug residues. The reliability of these tests were questioned at the 1991 meeting of the National Conference on Interstate Milk Shipments, the organization under which States monitor milk. At the meeting, Appendix N to the Pasteurized Milk Ordinance was passed. This appendix requires that all tankers of milk be tested for beta-lactam drug residues before being processed for food and that only tests found acceptable by the FDA be used in the monitoring of milk.

Through this cooperative program, 16 tests were accepted in 1994. All the tests have been for beta-lactam drugs. We are now evaluating tests for other potential residues in milk.

Also at this 1991 meeting, the NCIMS authorized a national program to compile results of residue testing by industry and regulatory agencies. FDA subsequently awarded a contract to develop a National Milk Drug Residue Data Base. The database was designed to promote maximum participation by the dairy industry to report on a voluntary basis all of their testing, without compromising any confidential data.

As of October 31, 1994, all fifty states and Puerto Rico were participating in the database program. However, it is important to recognize that this is a voluntary reporting program and the samples and tests reported

do not necessarily represent one hundred percent of the milk supply from every state.

The following is a short summary of the survey results. During the period October 1, 1993, to September 30, 1994, there were **4,179,108** milk samples analyzed for animal drug residues. Of these samples, **3,693** tested positive for a residue. A total of **4,589,085** tests were reported on the samples representing 14 different groups or families of individual drugs. Forty separate testing methods were used to analyze the samples for residues. Detailed information is available from CVM by calling (301) 594-5902.

Conclusion

CVM is in the process of implementing many changes. We realize that whatever changes are made must be scientifically relevant and legally sound if we are to maintain confidence in the drug approval process and, ultimately, the safety of milk, meat, and eggs. We are 100% committed to improving the availability of approved new animal drugs, but we all must realize that it will take cooperation among everyone associated with the use of animal drugs to bring about beneficial changes. CVM can be the catalyst to bring all the appropriate parties together and to coordinate their actions.

I want to convey to you our commitment to improve drug availability and improve communication between industry and the Agency. From pre-approval conferences with pharmaceutical firms, to adverse drug experience reporting, we hope to work more closely with our various constituencies to meet all our goals. We would like to hear your thoughts on these issues.

Abstract

Control of BSE: MAFF tightens up on feed production

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The Ministry of Agriculture, Fisheries and Food (MAFF), United Kingdom has announced 'a strengthening of the rules' for preventing tissue potentially infected with the BSE agent from entering the cattle feed chain. It also says that there is 'room for improvement' in the application of existing rules in some slaughterhouses, and that further action is under way to deal with this.

In answer to a written parliamentary question from Mr. Edward Garnier (Con; Harborough) on July 19, Mr. Douglas Hogg, the agriculture minister, said that the ruminant feed ban introduced in July 1988 had been successful in bringing the epidemic under control, as there were now 44.6 per cent fewer suspect cases being reported compared with the same period last year. However, he continued, there had still been cases of BSE in animals born after the ban, which suggested 'some continued leakage of BSE infective material into animal feed'. To date, 20,219 cases of BSE have been confirmed in cattle born after the feed ban, and MAFF attributes these cases to a food-borne source of infection.

At a press conference on the same day, the Chief Veterinary Officer, Mr. Keith Meldrum, said that MAFF's investigations had so far shown no evidence of maternal transmission of BSE. However, MAFF had found, when its Meat Hygiene Service took over control of slaughterhouses in April this year, that some 'fine tuning' of controls in slaughterhouses and processing plants was needed to prevent potentially infected material finding its way into cattle feed.