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Regulatory

Processing and evaluation of adverse drug experience reports at the Food and Drug Administration Center for Veterinary Medicine

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The FDA-Center for Veterinary Medicine (CVM) monitors reports of adverse drug experiences (ADE) for animal drug products, medicated feeds, and veterinary devices. An ADE is an undesired effect or lack of a desired effect. During 1997, the FDA-CVM received more than 4,000 reports. Every report is evaluated by a veterinarian and entered into a computer database. For instances in which public or animal health is judged to be at risk, the initial review leads to follow-up activity. The final result can be a product safety communication, change in labeling, or in rare circumstances, removal of the product from the market or even withdrawal of FDA approval to market the product.

Monitoring System

The purpose of the monitoring system is to detect unexpected problems associated with use of animal drugs. Detection of these unexpected events allows the FDA-CVM to achieve 3 program goals. The first goal is to provide an accurate product safety profile. Despite the highest standards for safety and effectiveness that exist for FDA approval, not everything is known about a drug when it is first marketed. Because of the limited size and controlled nature of premarketing clinical trials, only the most common adverse events will be observed and included in product labeling at the time of FDA approval. An accurate safety profile emerges only after a product is marketed and the number and spectrum of animals receiving the drug increases.

The second goal is to detect and provide information on unsafe use of products. Veterinarians often use products in species, or for indications, for which they are not approved. Typically, little safety information for these uses appears on the product label. Pharmacovigilance is an important tool in gathering safety information for extralabel drug use. In this context, pharmacovigilance refers to the generation, collection, maintenance, and evaluation of voluntarily contributed ADE information. Interaction of concurrently administered products is another area in which pharmacovigilance information is critical to the safe use of products. Although safety testing may be done for combination product approvals, and some limited voluntary testing of potentially concurrently used products may be performed, a general requirement for testing drugs that may be used concurrently does not exist. A substantial body of safety information exists for concurrent product use in human beings; however, similar information for animals is limited.

The third goal of the program is to provide an early warning system in rare instances in which contamination or manufacturing problems adversely affect product safety. This allows expeditious product recall, which minimizes harmful effects from unsafe products.

History

The reporting of ADE by veterinary medical professionals is entirely voluntary. However, federal regulations require drug manufacturers to forward to the FDA all information concerning ADE observations reported to their companies. In 1971, the FDA finalized regulations outlining the requirements of drug manufacturers to submit ADE for approved animal drugs. The legal definition of an ADE is any unexpected adverse effect, injury, toxicity, or sensitivity reaction associated with use of an animal drug regardless of whether it was determined to be attributable to the drug. The term “adverse drug reaction” was originally used but was changed to ADE because of the implication of a cause-and-effect relationship between a drug and an adverse effect before this relationship is established. The FDA-CVM generally restricts use of the term adverse drug reaction to situations in which reasonable evidence of a cause-and-effect relationship exists between the drug and the adverse effect. Lack of effectiveness is also considered an ADE. In 1971, ADE were reported, using form FDA 1932, the same form that is used today. During the subsequent decade, ADE were abstracted from ADE reports by FDA veterinarians and recorded for each drug. Formal means were not available for effectively analyzing data derived from reports.

In 1986, FDA-CVM veterinarians took advantage of emerging technology to develop an ADE computer database. Specific data elements needed for monitoring drug safety and effectiveness were selected to balance
the need for complete information with the limited responses generally available from a voluntary reporting system. The database design also involved in-house development of a standardized veterinary medical nomenclature system and modified use of a published algorithm to assess potential drug involvement. The new database allowed for prompt and efficient analysis of all adverse experience reports received by the FDA-CVM. Additionally, the database allowed the FDA-CVM to respond quickly to Freedom of Information requests and generate annual summaries of ADE reports for use by the veterinary and pharmaceutical communities.

Current Procedures
According to federal regulations for FDA-approved animal drugs, drug manufacturers must report ADE within 15 working days of receipt by the applicant if it includes information about unexpected effects (conditions not listed or addressed on product label), injury, or toxicity. Also, this 15-working day reporting requirement includes reporting unexpected increases in incidence of an expected adverse effect or an increase in severity of an ADE. Information concerning any unusual failure of a drug to induce expected pharmacologic activities must also be submitted within this 15-day period. All other suspected ADE reports may be submitted at 6-month intervals during the first year after approval and annually thereafter as part of the periodic drug experience report. The FDA-CVM's goal is to have the report reviewed and abstracted for analysis within 30 days. More serious adverse drug effects warrant expedited review.

Data Analysis
A modified algorithm1 is used to standardize criteria to assess whether an observed ADE was drug related. This exercise uses 6 standard questions designed to minimize arbitrary and subjective judgments. The questions address whether reported signs are consistent with known effects of the drug, whether there is any other explanation for the observation, the time between drug administration and observed effects, evidence of drug overdose, the effect of ceasing drug use, or “dechallenge” and the effect of reinitiating drug use, or “rechallenge.”

Decisions are made on the basis of evidence available at the time of review. If pertinent new information is assembled later, the algorithm may be reapplied. New information usually comes from a follow-up report submitted by the sponsor. Algorithm scores do not, by themselves, determine whether an adverse reaction will be included on the label of a drug product. The database allows the veterinary reviewer to analyze ADE data in various combinations. In determining whether a drug should be the subject of safety or efficacy concerns, the veterinary reviewer considers a number of factors, including whether the ADE is an unexpected effect not listed on the drug label, the seriousness of the ADE in adversely affecting animal health, the number of reports involving the specific adverse effect, the number of animals affected, geographic patterns, other signalment or zoographic patterns, and whether the association of the drug with the ADE is biologically plausible.

Using these factors, the veterinary reviewer identifies those suspected drug-related ADE and forwards these suspicions for potential evaluation by the FDA-CVM Monitored Adverse Reaction Committee (MARC). The MARC further evaluates the scientific basis of the reviewer's suspicions and formulates recommendations for any necessary actions. Depending on the nature of the ADE, MARC recommendations can involve label changes and product recalls, or the MARC may request more information, including possible additional studies from manufacturers. At times, on the committee's recommendation, the FDA-CVM may require the involved drug manufacturer to issue a “Dear Doctor” letter to veterinarians, informing them of any drug problems. In rare instances, the drug may be removed from the market.

A key limitation of any voluntary reporting system is the inability to accurately characterize the population in which the drug is being used. The under-reporting of ADE and problems with report quality further limit the FDA-CVM's ability to assess the extent of any real safety or efficacy problems. Additionally, drug administration practices generally are not included in medical records.

These limitations aside, the factors listed do allow the FDA to characterize unexpected ADE and identify situations of product failure resulting from product defects or formulation changes. Pharmacovigilance is necessary to allow the FDA to fully describe the safety and efficacy of drugs that were approved on the basis of results of research studies that involved limited numbers of animals under limited conditions of drug use.

Recent and Future Improvements
More recently, the FDA-CVM has initiated a number of changes to improve processing of ADE reports. Some of the changes have included the following:

▶ Redesign of the ADE computer database to the ORACLE database platform. The revised database will include enhancements of required data fields and automatic data quality assurance. The database will ultimately be integrated into the FDA-CVM corporate database to increase data accessibility by all FDA-CVM personnel.

▶ Redesign of the ADE review process through employment of a staff dedicated primarily to ADE review. The FDA-CVM has recently employed several veterinarians on a part-time basis, most of whom are also currently in clinical practice, to evaluate ADE reports.

▶ The FDA-CVM is committed to making ADE reporting easier for veterinarians. Veterinarians are encouraged to report drug problems directly to drug manufacturers, because manufacturers have a vested interest in ensuring drug safety and efficacy. However, in the event that practitioners prefer reporting directly to the FDA-CVM, reports will be accepted by telephone, mail, or facsimile. The FDA-CVM shares all directly received reports with manufacturers to facilitate investigation of reports.
The FDA-CVM withholds the reporting veterinarian's name if directed to do so; however, this can substantially limit the manufacturer's ability to investigate the ADE report.

- **Recognition and incorporation of the United States Pharmacopeia (USP) Practitioner Reporting Network (800/4-USPPRN).** Although the FDA-CVM suggests that veterinarians report ADE directly to drug manufacturers to ensure that they obtain fullest support, it also recognizes that many practitioners prefer to report to a party other than drug manufacturers or the FDA. In addition, USP facilitates reporting when it is not apparent which regulatory agency (USDA, Environmental Protection Agency [EPA], or FDA) has responsibility for a product by providing a single processing point for all animal health product adverse event reports. The FDA-CVM supports the USP and the AVMA in their efforts to encourage veterinarians to report suspected adverse drug experiences.

- **The FDA-CVM will continue activities to increase veterinarians' awareness of the existence of the ADE program and the importance of veterinary participation.** A toll-free number has been established for reporting ADE (888/FDA-VETS) and postage is paid for ADE reporting forms, which can be obtained free on request. The FDA-CVM developed a brochure describing the ADE program and is attempting to ensure that all senior veterinary students receive the brochure. It also is increasing program awareness, as resources permit, through talks at major veterinary conferences and through journal publications. Finally, the FDA-CVM is disseminating a summary of all ADE reports by publication in the FDA Veterinarian and electronically via the FDA-CVM World Wide Web site (http://www.fda.gov/cvm), the Member Only Center of the AVMA Network (http://www.avma.org), and the Veterinary Information Network (http://www.vin.com).

**Future Challenges and Opportunities**

Just as practicing veterinarians are expected to meet a high practice standard, they and their clients expect animal health products to meet a high standard. These expectations provide challenges and opportunities for the animal health industry and regulatory agencies.

- **Animal health products** are marketed worldwide and are the subject of myriad regulatory requirements, including reporting of adverse experiences. Lack of standard nomenclature hampers the sharing and use of this information by regulatory agencies. These problems, as well as differing national reporting requirements, complicate the task of reporting adverse experiences to regulatory authorities for industry.

- **The FDA** is responsible for regulating all medical products for use in human beings. All reports of ADE, regardless of whether they are associated with drugs, devices, biologics, or product incompatibility arising from concurrent use of multiple products, are reported to the FDA. This simplifies reporting, allows harmonization of reporting requirements and efficiency of report processing, and facilitates investigation of potential product interactions. Animal health products, on the other hand, are regulated by 3 federal agencies; the FDA regulates drugs and devices, the EPA regulates pesticides, and the USDA Animal and Plant Health Inspection Service regulates biologics. These federal agencies' regulations and priorities are different. Consequently, fewer opportunities to harmonize requirements, simplify reporting, and increase efficiency of report processing are available. Identifying product interactions also is far more challenging. Despite this limitation, staff members involved in monitoring of marketed products from each agency are in communication with each other and with the USP regarding ADE issues.

- **Underreporting by veterinarians and report filtering by manufacturers reduce effectiveness of the ADE reporting program.** Although the FDA-CVM, the USP, and the AVMA have taken steps to make reporting easier for veterinarians, a professional commitment to sharing information with colleagues is still the key factor in voluntary reporting. Only when a substantial percentage of veterinarians is willing to take the time to report ADE will the ADE reporting program be fully effective.

- **Suspicion that all ADE reports submitted by veterinarians to manufacturers are not, in turn, submitted by manufacturers to the FDA-CVM (report filtering) is a contributing factor to underreporting.** Although filtering is rarely done by most manufacturers, in some limited instances it has occurred, particularly when the manufacturer makes the assumption that the product did not cause the ADE. The ADE reporting program will be limited in effectiveness if manufacturers investigate and submit reports to the FDA-CVM on only selected ADE reports. Consequently, FDA regulations for manufacturers require that all ADE reports be submitted to the FDA-CVM, regardless of whether it was determined to be attributable to the new animal drug. This regulation relieves manufacturers of the burden of justifying their decision to not submit an ADE report to the FDA-CVM and the FDA-CVM of the burden of interpreting data confounded by this type of reporting bias. It also fosters an atmosphere of trust and cooperation between veterinarians, manufacturers, and the FDA in which full reliance can be placed on science in determining causality of adverse events. The ADE reporting program will be most effective when veterinarians are fully active in reporting ADE and manufacturers maintain a high degree of fidelity in investigating and transmitting these ADE reports to the FDA-CVM.

Identifying and implementing solutions to these challenges will substantially improve the availability of product safety information to veterinarians and improve manufacturers' and regulatory agencies' effectiveness in responding to customers' needs.

The FDA-CVM seeks to ensure that safe and effective drugs are marketed. Therefore, the FDA-CVM is...
committed to encourage ADE reporting and to disseminate all information obtained back to the veterinary profession. We encourage veterinarians to take an interest in any unintended responses to drugs administered and to share their observations with their colleagues through the reporting process. Veterinarians should understand that reporting suspected ADE is not likely to result in the removal of an animal drug from the market. The most common result, by far, would be an improved label that includes the new information.

Reference