AVMA American Veterinary Medical Association

1931 N. Meacham Rd.
Suite 100
Schaumburg, IL
60173-4360

phone 847.925.8070
800.248.2862
fax 847.925.1329
www.avma.org

September 1, 2009

Dr. Theresa Toigo
Director, Office of Special Health Issues
Office of Scientific and Medical Programs
Food and Drug Administration
5600 Fishers Lane, Room 9-49
Rockville, MD 20857

Dr. Doug Throckmorton
Deputy Director, Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Facility
10903 New Hampshire Avenue
Building 51, Room 6133
Silver Spring, MD 20993

FDA Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs

Dear Drs. Toigo and Throckmorton:

I am writing on behalf of the American Veterinary Medical Association (AVMA), established in 1863 and the largest veterinary medical association in the world. As a not-for-profit association established to advance the science and art of veterinary medicine, the AVMA is the recognized national voice for the veterinary profession. The association's more than 78,000 members comprise approximately 85% of U.S. veterinarians, all of whom are involved in a myriad of areas of veterinary medical practice including private, corporate, academic, industrial, governmental, military, and public health services.

On February 9, 2009, the Food and Drug Administration (FDA) announced its plans to exercise its new authority to require a Risk Evaluation and Mitigation Strategy (REMS) for many of the opioid drug products. The FDA may require a REMS when FDA determines that a REMS is necessary to ensure the benefits of a drug outweigh the risks associated with the drug. The FDA's goal is a single REMS for all opioid drug products. The AVMA questions whether a single REMS is appropriate for all applications.

We recommend that all DEA-registered, licensed veterinarians continue to have access to sustained-release opioid products labeled for use in humans, to relieve animal pain and suffering. It would be most expeditious to exempt veterinarians from any REMS that would prevent veterinary therapeutic access to sustained-release opioids.

General Comments

The AVMA acknowledges the efforts by the FDA to examine the benefits and risks of certain opioid medications for use in human medicine. Certainly we understand the FDA's concern and its need to assure safety of opioids use in people.

The AVMA asserts the risks posed by veterinary use of opioids are small, as we believe that there is little misuse and/or misprescribing of opioids by veterinarians. In addition, animal health and welfare is not compromised by current veterinary medical administration of sustained-release opioids. Further, we are unaware of diversion being a significant concern in veterinary medicine. Among all the health professions under DEA registration, veterinary medicine falls low in the list of diversion concerns.

Presently, there are an insufficient number of approved animal drugs labeled for the many species and conditions veterinarians must treat. The administration of human drugs by a veterinarian to animal patients is tightly regulated by the FDA as codified by the Animal Medicinal Drug Use Clarification Act (AMDUCA).

The FDA's current activities to examine the benefits and risks of opioid products in human medicine are laudable; however, veterinarians cannot prescribe drugs for use in people, and the AVMA cautions against the unintended consequences of REMS designed specifically for human medical purposes that would result in denied access to veterinarians in their treatment of animal patients.

When an analgesic medication is needed for an animal patient opioids are often not the initial drug of choice; however, in some instances these medications are highly indicated; especially in the treatment of animals with severely painful conditions, including but not limited to pain associated with major orthopedic events, invasive surgical procedures, and cancer. In other instances, opioids are used in animals for sedative purposes, especially when age, health, and therapeutic restraint measures warrant precautionary approaches in animal patients.

Specific Observations and Findings

The AVMA's volunteer leadership represent a cadre of experts across multiple board specialties and species groups:

- Pharmacology and clinical pharmacology
- Epidemiology
- Microbiology
- Immunology
- Industry
- General small animal medicine and practice
- Feline medicine
- Bovine medicine
- Poultry medicine
- Swine medicine

- Equine medicine
- Zoo and wildlife medicine
- Small ruminant medicine

These experts examined the occurrence and extent of veterinarians misprescribing and/or misusing opioid drugs and whether use of sustained-release opioids has negatively impacted animal health and welfare. Specifically the AVMA's Council on Biologic and Therapeutic Agents (COBTA), and its Clinical Practitioners Advisory Committee (CPAC) closely evaluated the issue and in their experiences have found that current veterinary medical administration of sustained-release opioids labeled for use in humans has not threatened the health and welfare of our animal patients.

The COBTA and CPAC evaluated several aspects of how veterinarians administer opioids and whether restricted access to opioids would have consequences on the practice of veterinary medicine:

Clinical veterinary medical uses of sustained-release opioids
The opioid products cited for a REMS process that are currently used in animals include, but are not necessarily limited to, fentanyl transdermal patches, oral methadone, and oral morphine.

Veterinarians administer sustained-release opioids for particularly painful conditions in various species and treating various medical conditions. In particular, transdermal fentanyl is used in severely painful animals, especially in trauma patients and in patients suffering with pain associated with cancer and orthopedic pain, both in post-operative care and in out-patient pain control. Fentanyl is also an important therapy when pain has become refractory in animals. To help prevent misuse, references such as the Plumb's Veterinary Handbook by Dr. Donald Plumb provide client education information about side effects and proper use for the veterinarian to relay when dispensing or prescribing fentanyl.

While methadone is used primarily as an injectable, oral methadone has been used successfully, considering its synergism with other opioids, especially in refractory pain associated with chronically painful conditions. In addition, methadone is used frequently in wildlife and zoo animals, particularly reptiles. Oral morphine is used for mild to severely painful conditions, and is also antitussive, antidiarrheal, and is used as a sedative.

Extended-release morphine tabs are especially helpful for zoo patients in providing longer term analgesia, which is important for the health and welfare of the patients, the safety of these undomesticated animals, and the safety of the workers handling such patients.

When a veterinarian develops a treatment plan for a patient, the veterinarian considers how the treatment will impact (both positively and negatively) the patient, the animal owner(s), and the environment. A veterinarian is trained to weigh the benefits and risks of certain treatments before prescribing and/or dispensing them. When a veterinarian determines that an opioid is medically necessary in a patient, s/he is taught to thoroughly explain to the animal owner if/how to administer the medication, what adverse effects to monitor for, and the need for the client to contact the veterinarian for follow-up with any questions or concerns.

Evaluation of veterinary medical prescribing/administration practices of sustained-release opioids

The COBTA and CPAC evaluated the current prescribing practices of sustained-release opioids, and they determined that current prescribing has not yielded negative impacts on animal health and welfare. These determinations are underscored by the relative lack of adverse event reports found on the FDA Center for Veterinary Medicine website.

Idiosyncratic reactions to sustained-release opioid administration are possible, especially due to relative lack of pharmacokinetic data of administration of these drugs, which have differing bioavailabilities, to the varying species and disease conditions treated by veterinarians. Clinically, however, our COBTA/CPAC have not found any dramatic adverse events associated with sustained-release opioids in their specialties and disciplines. Some professional organizations recommend as a first treatment modality those opioids that typically cause fewer reactions in certain species, to err on the side of caution. Refractory pain, lack of effect from first-use opioids, and severely painful conditions sometimes still require the need to administer more potent opioids such as fentanyl.

Adverse events associated with veterinary medical administration of sustained-release opioids

Upon evaluating the possible adverse events that could result from use of opioids in animal patients, the COBTA and CPAC do not believe there should be any blanket species preclusions for treatment with certain opioids. Above all, veterinarians are trained to "do no harm" when contemplating treatments for their patients, and part of the evidence-based benefit/risk analysis incorporates evaluation of current scientific data and case studies, and obtaining advisement from esteemed experts. These evaluations, coupled with the current clinical situation and the abilities of the owner(s) to medicate the animal(s), are all considered when deciding which particular treatment is best for an individual patient.

It is important to note that veterinarians gain continuing education on how to appropriately use opioids in their daily course of practice, both through professional organizations and through scientific conferences:

- Professional organizations, such as the American Animal Hospital Association and the American Association of Feline Practitioners, have developed guidelines on the recommended first-use opioids and potential side effects associated with particular opioids in small animals. These types of guidelines are provided for veterinarians working with various species and specialties.
- Conferences such as the AVMA Annual Meeting, Western Veterinary Conference, and the Central Veterinary Conference provide opportunities for veterinarians to gain continuing education on current medical practices and new therapeutic options.
- Widely distributed scientifically reviewed publications are shared with AVMA members through the Journal of the AVMA.

The benefit of veterinary access to human-label opioids greatly outweighs the risk associated with the potential for adverse events in animals, despite the fact that opioids labeled for use in people do not have safety/efficacy data for use in animals like opioids labeled for animals would have. The ability to utilize human-labeled opioids is paramount, considering the varying species and disease conditions veterinarians treat. In the absence of adequate drugs labeled for use specifically in

animals, the AMDUCA is critical because it provides veterinarians with a greater number of tools to use to relieve pain and suffering in their animal patients.

Veterinarians are encouraged to report adverse events, so that the federal agencies with oversight over animal health products can determine if there is a trend showing significant adverse events. The AVMA has worked to promote adverse event reporting by veterinarians through our efforts with not only FDA and its new MedWatch web portal, but also with the Environmental Protection Agency and the United States Department of Agriculture. We believe veterinarians do report suspected adverse events to either the manufacturers or the federal agencies with oversight. Upon accessing the current adverse events reporting site at the FDA CVM website on August 21, 2009, we found only a handful of adverse event reports associated with opioids, from 1987 to the present time.

Current access to sustained-release opioids by veterinarians

At present, veterinarians who dispense sustained-release opioids either obtain their opioid products through veterinary distributors, or veterinarians who administer sustained-release opioids less frequently will often provide written prescriptions for their clients to fill at a pharmacy of the client's choice.

Veterinarians who administer sustained-release opioids comprise both practitioners within regular veterinary clinics, and practitioners at major veterinary teaching hospitals/specialty clinics. Because of the wide species and conditions treated by veterinarians, veterinarians across all types of practices need access to these opioids, either through direct dispensing or, as applicable, written prescriptions.

It is important to note that transdermal fentanyl patches are typically administered to the patient by the veterinarian within the clinic setting. A large number of patients needing fentanyl patches are in-patients that are in critical care and/or post-operative. However, for those patients needing pain control at home (for example, oncology patients), because of the risk of fentanyl effects that could result from inappropriate handling by the client, veterinarians typically apply the patch, and depending on the location of the patch, will encompass the patch in a bandage to limit access by both owner and animal.

Implications of previously restricted drug access on veterinary medicine

Veterinarians are currently affected by restricted drugs currently available only to certain practitioners, namely isotretinoin. Prior to restriction, administration of isotretinoin was found to be successful for treatment of certain dematologic diseases including sebaceous adenitis and intracutaneous follicular cysts. However, due to the restriction of isotretinoin availability through the iPLEDGE program, veterinarians no longer have access to this drug. Accessibility to isotretinoin would provide another tool for veterinarians to consider in treating certain conditions in their patients, particularly for veterinarians board certified in dermatology and/or oncology.

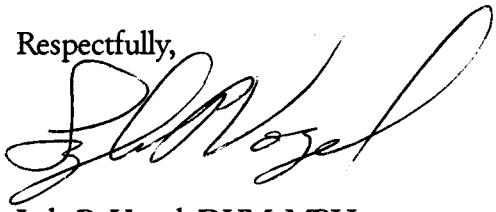
However, because this drug has such a specific need within a veterinary specialty, the implications of isotretinoin's restricted access in no way can be compared to the anticipated consequences that would result if the same restrictions were placed on veterinary medical access to sustained-release opioids. The needs for isotretinoin are limited, whereas the needs for sustained-release opioids is as diverse as the number of species and conditions veterinarians treat to relieve animal pain and suffering.

In conclusion:

- There are an insufficient number of approved animal drugs labeled for the many species and conditions that veterinarians treat; consequently, the administration of human drugs by a veterinarian to animal patients is tightly regulated by the FDA and codified by the Animal Medicinal Drug Use Clarification Act (AMDUCA).
- We recommend that all DEA-registered, licensed veterinarians continue to have access to sustained-release opioid products labeled for use in humans, to relieve animal pain and suffering.
- We believe it would be most expeditious to exempt veterinarians from any REMS that would prevent veterinary therapeutic access to sustained-release opioids.

The AVMA appreciates the opportunity to comment and would like to continue the dialog on this and other important matters. We also would welcome the opportunity to further provide our insights and feedback. For further clarification on the AVMA's comments, please contact Dr. Lynne White-Shim at 800-248-2862 ext. 6784, or at lwhite@avma.org.

Respectfully,



Lyle P. Vogel, DVM, MPH
Assistant Executive Vice President
American Veterinary Medical Association

cc: Dr. Bernadette Dunham, Director, FDA Center for Veterinary Medicine
Dr. John K. Jenkins, Director, Office of New Drugs, FDA CDER
Dr. Deborah J. Miller, Health Programs Coordinator, Office of Special Health Issues, Office of the Chief Scientist
Ms. Anne M. Henig, Regulatory Health Project Manager, FDA CDER