Regulatory Framework for the Availability and Use of Animal Drugs in the United States

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INTRODUCTION

Given the relatively limited number of approved animal drugs available to veterinarians, practitioners often rely on the use of various types and sources of drugs to treat their patients. Some of these products may be unapproved for human and/or animal use, they may be unsafe or have no discernible clinical effect, or they may lack a solid pharmacologic basis for their use. Only when buying animal drugs approved by the US Food and Drug Administration (FDA) are practitioners assured of the product safety, effectiveness, and manufacturing to the strict standards for quality, purity, and potency. However, even when using approved veterinary products, companion animal veterinarians may not always be aware of the specific condition(s) of use for which

Disclosures: The author has nothing to disclose.
This article represents a compilation of information available in a variety of documents available on the CVM Web site (http://www.fda.gov/AnimalVeterinary/default.htm) and the original material by the author. The reader is encouraged to visit the Web site for more detailed information on each of the topics covered in this article.
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KEYPOINTS

Use by veterinarians of animal drugs approved by the Food and Drug Administration (FDA) is the only way to be assured of product safety and efficacy, truthful and complete labeling, and appropriate manufacturing standards.

Statements made on product labels or Web sites such as “made in an FDA-registered facility” or “registered and listed with the FDA” does not mean that product is an FDA-approved drug.

FDA-approved drugs can be identified by searching the online database Animal Drugs @ FDA or by identifying the 6-digit NADA or ANADA number on the product label.
a drug is approved, such as the indication(s), dose and dosing regimen, target species, and route of administration. Because of these conditions of use, a product approved, for example, for the treatment of skin infections associated with specific susceptible bacteria indicated on the label may not be effective for treating other types of infections, or the dose for other infections may not be adequate. In addition, if a higher dose or a different dosing regimen is used than is stated on the approved product label, there is an increased risk of toxicity, as the safety has not been evaluated at those higher doses and/or more frequent dosing regimens.

It may be difficult for practitioners to recognize the differences between approved and unapproved drugs (or uses), and understand and appreciate potential risks associated with the use of unapproved or approved products used outside of the approved label conditions. The risks may range from mild adverse reactions or poor efficacy response to life-threatening toxicity or complete lack of effectiveness, both of which may ultimately result in the patient’s harm. Therefore, it is critical for practitioners in modern veterinary practice to not only use and understand drug labels and how they may affect their patients, but also to check them periodically for updates of important safety information.

The goal of this introductory article is to help practitioners understand the basis for the approval of new animal drugs, the terminology and specific meaning of terms related to the approval, and the marketing and use of veterinary drugs in companion animal practice.

The FDA Center for Veterinary Medicine (CVM) regulates the manufacture and distribution of drugs and food additives that will be given to animals. Animal drugs are regulated under The Federal Food, Drug, and Cosmetic Act (FFDCA; the Act), which provides the statutory provisions governing the regulation of veterinary products. The Act defines the term drugs, in part, as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” Under the Act, a new animal drug is considered to be unsafe unless there is an approved New Animal Drug Application (NADA) or Abbreviated New Animal Drug Application (ANADA) under section 512 of the FFDCA, a conditional approval under section 571, or an index listing under section 572.

REGULATORY PATHWAYS FOR APPROVAL OF NEW ANIMAL DRUGS

There are several different legal pathways for the approval of animal drugs. Drugs can be approved by submitting a NADA and obtaining a new animal drug approval, or by submitting an ANADA and obtaining a generic animal drug approval. The FDA’s approval means the drug is safe and effective when it is used according to the label; its strength, quality, and purity are consistent from batch to batch; and its labeling is truthful and complete.

Before a new animal drug is approved, the sponsor must establish, among other things, that the drug is safe and effective for the intended use, that its manufacturing complies with quality requirements, and that the labeling is truthful and complete. There are 6 data elements (commonly referred to as technical sections) that must be completed for a new companion animal drug approval: Effectiveness; Target Animal Safety (TAS); Chemistry, Manufacturing, and Controls (CMC); Environmental Safety; All Other Information; and Labeling. Approved new animal drugs can be categorized as either brand name or generic.

- A brand-name (pioneer) new animal drug is an original FDA-approved new animal drug marketed under a proprietary, trademark-protected name. The new animal
drug approval process includes a detailed and comprehensive review of all the submitted data as described above (recently reviewed by Smith and Modric, 2013¹). The process is very similar for drugs intended for food-producing and companion animals, with the exception that a human food safety evaluation is not required for drugs intended for use in companion animals. After an approved brand-name animal drug has been on the market for a specific number of years, another drug sponsor can start the approval process for a generic copy by submitting an ANADA.

- A generic new animal drug is a copy of an approved new animal drug that has been previously approved and shown to be safe and effective when used in accordance with its labeling. For the approval of a generic animal drug, the information in the ANADA must show that the active ingredients of a generic animal drug are the same as those of the approved product and that it is bioequivalent to the approved animal drug product. The finished product must also be the same strength and dosage form, with the same route of administration, as the approved product. The application is “abbreviated” because generic copies of brand-name animal drugs go through a shortened drug approval process, allowing sponsors to fulfill TAS and effectiveness requirements through the demonstration of product bioequivalence (established in 1988 by the Generic Animal Drug and Patent Term Restoration Act). Similar to the brand-name drug approval, the information in the ANADA must also show that the generic copy is consistently made from batch to batch and that the labeling for the generic copy must match the labeling for the approved brand-name animal drug, except for a few allowable differences (e.g., a different trade name).

Once approved, both brand-name and generic animal drugs can have subsequent supplemental approvals that legally extend an approved product’s conditions of use. Supplemental new animal drug applications allow companies to make changes to an approved product while relying on the existing approval for some of the application requirements. Depending on the type of changes proposed in supplemental applications, new effectiveness and TAS data may or may not be required. Minor changes (such as a change in container style, shape, size or components; a minor change in the manufacturing processes; the addition of an alternative manufacturer) do not require additional safety and/or effectiveness information. By contrast, major changes (such as a change in dose or treatment regimen, the addition of a new species, or the addition of a new claim) can affect the safety and/or effectiveness of the new animal drug, and thus need to be evaluated before supplemental approval and indication on the new label. This new labeling information may be of great importance to practitioners when selecting drug treatment for their patients because of new effectiveness and/or safety information.

The FDA is responsible for determining the marketing status of animal drug products based on the ability to provide adequate directions for safe and effective use of the product by a lay person:

- **Prescription** (Rx) products can be dispensed only by or upon the lawful written order of a licensed veterinarian.
- **Over-the-counter** (OTC) drugs have labels written so that the layman can use a drug safely and for the purposes for which it is intended (adequate directions for use).
- **Veterinary Feed Directive** (VFD) is a written statement issued by a licensed veterinarian to authorize the client to obtain and use the VFD drug in or on animal feed in accordance with the directions for use approved by the FDA.
The same drug substance can be approved and marketed in several different dosage forms, intended for use by different routes of administration and in different species of animals. Therefore, the same drug substance may be distributed OTC for one use or application and by prescription use only for another use or application. In addition, the marketing status may change after the initial approval, thus encouraging practitioners to regularly check drug labeling.

MINOR USE AND MINOR SPECIES CONSIDERATIONS

Animal drugs intended to be used in minor species and/or for minor uses have additional unique aspects for approval and marketing. Many of these drugs came into being through passage of The Minor Use and Minor Species (MUMS) Animal Health Act of 2004. This law is intended to encourage pharmaceutical firms to make more medications legally available to veterinarians and animal owners, to treat minor animal species and uncommon diseases in the major animal species. The legal definition of minor species in the United States includes all species other than humans and the major species (ie, cattle, horses, swine, chickens, turkeys, dogs, and cats). “Minor use” (in major species) is defined as diseases that occur infrequently or in limited geographic areas and in only a small number of animals annually. The “small number” for each of the major species is defined by regulation.

A common challenge for drug approvals in minor species is the animal diversity (eg, zoo animals, ornamental fish, parrots, ferrets, guinea pigs) and the limited number of animals that can be used in effectiveness and safety testing. In addition, there is a vast difference in animal care and management, diseases, and inherent sensitivity to or toxicity of pharmaceutical products. Many of these same limitations apply to the uncommon diseases or conditions in the major species.

The MUMS Act provides several innovative ways to encourage development and approval/marketing of drugs used either in minor species or to treat uncommon diseases in major species. Although many drugs may be available to veterinarians under the extralabel drug use (ELDU) provisions, they are not approved for these particular uses. Effectiveness and safety information for the ELDU is not available for the specific unique use, but would become available through the MUMS approval process. Also, many minor species are most effectively treated using medicated feeds, which are not permitted to be used outside their labeling.

Minor use/minor species animal drugs are eligible to complete a Conditional New Animal Drug Application (CNADA), and can obtain a conditional approval. This process has the same approval requirements as the NADA process with the exception of effectiveness. For a new animal drug application, the effectiveness has to be demonstrated before drug approval through independent substantiation in adequate and well-controlled studies (Code of Federal Regulations, 21 CFR 514.117) and by providing valid inferences to the target population (inferential value). For a conditional approval, however, drugs have to demonstrate a reasonable expectation of effectiveness. Following conditional approval, drugs can be legally marketed for up to 5 years, through annual renewals, while collecting the remaining required effectiveness data to fulfill all NADA requirements.

Another process unique to MUMS drugs, Designation, is an incentive program that encourages development of drugs for minor species or rare diseases. Sponsors of “designated” new animal drugs are eligible to apply for grants to fund safety and effectiveness studies, and also receive 7 years of exclusive marketing rights for the designated use of their new animal drug beginning on the date of approval or conditional approval.
Yet another unique and innovative approach that the MUMS Act provides is legal marketing of some unapproved new animal drugs for non–food-producing minor species, based largely on a scientific evaluation of effectiveness and safety by an outside expert panel. Drugs in this category may be added to the *Index of Legally Marketed Unapproved New Animal Drugs for Minor Species* (the Index). Indexed drugs, although not approved, provide specific information for practitioners and users regarding the dose, indications, and safe use of such products. This process is easier and less costly for sponsors interested in achieving legal marketing status for products for minor species (eg, zoo animals, ornamental fish, reptiles, caged birds), for which the approval process would likely be cost-prohibitive and/or impractical owing to the scarcity and inherent value of the animals.

**EXTRALABEL DRUG USE**

ELDU refers to the use of an approved drug in a manner that is not in accordance with the approved label indications. Until the passing of the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), the ELDU of new animal drugs was considered illegal, and the FDA exercised enforcement discretion under certain circumstances. AMDUCA amended the FFDCA to allow for ELDU by or on the order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship under certain conditions.

ELDU is common in companion animal practice because the number of available approved animal drugs is relatively small, and those that are approved are approved for specific conditions of use. Drugs can be used in an extralabel manner if there is no animal drug approved for the intended use; an animal drug is approved but in a different dosage form or concentration; or the approved drug has been found to be clinically ineffective when used as labeled. However, in any case, the product used in an extralabel manner has to be an FDA-approved (human or veterinary) drug.

Veterinary involvement is required for ELDU because there is no direct evidence of the safety and effectiveness of the drug for the unapproved indication, dose, species, and so forth. When a drug is used by or under the supervision of a veterinarian, it decreases potential risks of toxicity and/or lack of effectiveness associated with ELDU. Therefore, a veterinarian is needed to not only diagnose a disease and make the optimal therapeutic selection for a specific individual patient, but also to continue monitoring the animal’s progress and make necessary adjustments. Veterinary involvement is particularly critical for animals for which there is a dearth of approved products and a general lack of understanding as to how such products may be used safely and effectively (eg, zoo animals, exotic pets).

**UNAPPROVED VERSUS APPROVED DRUGS**

Unapproved animal drugs include traditional drugs used in veterinary practice (some injectable vitamins, medicated shampoos, intravenous glucose solution, antidotes, and so forth), animal supplements, homeopathic remedies, other complementary/alternative medicine products, and products compounded from bulk. The problems with using unapproved products are that: (1) they are not reviewed by the FDA and may not meet the FDA’s strict standards for safety and effectiveness; (2) they may not be labeled or advertised appropriately or truthfully; and (3) manufacture of these products may not maintain the drug’s quality, purity, and consistency. In addition, any safety, effectiveness, and/or manufacturing problems with these drugs are difficult to identify because there are no reporting requirements of adverse drug events for
unapproved animal drugs. By contrast, as part of the FDA’s continued monitoring of
safety and effectiveness, drug companies are legally required to report to the FDA
all adverse drug events that occur after the drug is approved. The required reporting
of adverse drug events allows the FDA to more easily identify problems and provide
additional labeling language or to take other safety measures (as deemed necessary)
after a drug is approved and used in a large number of patients. Such safety moni-
toring throughout the life cycle of a drug is not available for drugs that are not
approved by the FDA.

The goal of the FDA-approval process is to protect animals and humans from
unsafe, ineffective, and/or substandard products by providing safe and effective
approved products. Drug companies that make and sell unapproved animal drugs
potentially put the health of animals (and perhaps people) at risk. Veterinarians can
decide whether the risks of using such products outweigh the expected benefits,
but the risk-to-benefit evaluation should be based on the knowledge and understand-
ing of the drug being used as well as its source. Practitioners selecting an FDA-
approved drug can have confidence that the drug will have the effect it purports to
have on the labeling. Using FDA-approved drugs decreases the health risks associ-
ated with unapproved drug use.

There are multiple ways practitioners can tell whether the product they are using is
approved or not:

- All FDA-approved animal drugs have a 6-digit NADA or ANADA number on the
  label. The statement “Approved by FDA” is usually on the drug label.
- Most prescription and over-the-counter FDA-approved animal drugs are listed in
  a searchable online database, Animal Drugs @ FDA. The database allows one to
  search using several parameters, including proprietary name (trade name), active
  ingredient, application (NADA or ANADA) number, dosage form, species, and
  indications.
- Most FDA-approved animal drugs are also included in the “Green Book,” another
  database available on the CVM Web site, which is updated monthly.

There are several common misconceptions among veterinarians about the approval
status of animal drugs available in veterinary practice. For example, the presence of a
National Drug Code (NDC) number on an animal drug label does not mean that the
drug is approved by the FDA. Similarly, the statement “Caution: Federal law restricts
this drug to use by or on the order of a licensed veterinarian” does not mean that it is an
FDA-approved drug. Furthermore, manufacturers of unapproved drugs may put other
statements on their label that may suggest that their products are approved, such as:
“Registered and listed with the FDA”; “Made in an FDA-registered facility”; “Made in
an FDA-inspected facility”; “Made in an FDA-approved facility.” None of these state-
ments mean that the product is approved by the FDA, but because they contain the
abbreviation FDA, they are misleading and are commonly interpreted as “FDA
approved.”

Finally, when choosing pharmacologic treatment for their patients, practitioners
should also be aware of long-term effects of using unapproved animal drugs on
veterinary practice and animal health. Drug companies that make and sell these unap-
proved animal drugs compete against drug companies that spend time and financial
resources on seeking approval from the FDA. If the market is full of unapproved drugs,
drug companies may be less willing to obtain approval for animal drugs. Ultimately,
this may result in a decreased availability of safe and effective new animal drugs in
the United States.
POSTAPPROVAL MONITORING AND REPORTING OF ADVERSE DRUG EXPERIENCE

Monitoring of veterinary drugs to assure their continued safety and effectiveness is one of the critical roles of the CVM. Evaluation of drug safety and efficacy continues throughout a drug’s life cycle through postapproval adverse drug experience (ADE) reporting to the FDA, which is mandatory for sponsors marketing approved animal drugs. The primary purpose of the CVM ADE database is to provide an early warning or signaling system to the CVM for adverse effects not detected during premarket testing of FDA-approved animal drugs.

Adverse drug experience includes, but is not limited to: (1) An adverse event occurring in animals in the course of the use of an animal drug product by a veterinarian or by a livestock producer or other animal owner or caretaker; (2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness); and (3) An adverse event occurring in humans from exposure during manufacture, testing, handling, or use of a new animal drug. (21 CFR 514.3)

Inclusion of a good medical history, all concomitant medications the animal is on, any recent surgical procedures, and as many clinical findings as possible helps the FDA evaluate the reported ADE to determine how likely it is to be drug related. Clinical findings including veterinary examination, clinical chemistries, complete blood counts, urinalysis, fecal examinations, radiographic results, and hemodynamic data such as blood pressure, any other pressure measurements in or around the heart, and neurologic assessments are all helpful in the assessment of each individual report.

Data on adverse events do have limitations because of various possible confounding factors that may play a role in reported toxicity or ineffectiveness. Factors such as concomitant medications, preexisting medical conditions, environmental conditions, and unapproved use of FDA-approved drugs (e.g., different dose, dosage regimen, and/or species) need to be considered when determining whether the adverse effect may be correlated with the drug treatment. Because ADEs are reported from animal populations of uncertain size, it is not possible to reliably estimate incidence rates. Although drug companies report the quantity of drugs marketed each year, it is not possible to determine the actual number of animals treated (because most small animal drugs are administered on an mg/kg basis), which would provide a better estimate of drug use.

Despite its limitations, the monitoring and evaluation of ADE reports is critical for ensuring adequate drug performance and preventing adverse health effects in animals. The CVM publishes a cumulative summary of ADE reports with a listing of clinical signs reported for each active ingredient in the database. Clinical signs are listed in order from most frequently observed to least frequently observed, by species and route of administration. This information can be very useful for clinicians, especially regarding new drugs, because the signs are reported much more quickly than any label changes can be made. By regularly checking the ADE report summaries veterinarians can be alerted early about potential safety concerns, and can decide to reconsider their drug selection or monitor their patients more closely. Although the ADE reporting cannot be used to estimate incidence rates or drug risk (because there is no accurate way to determine how many animals were given the drug), the frequency of reported signs will alert practitioners to pay particular attention to specific types of adverse events.

The CVM encourages veterinarians and animal owners to be vigilant and active participants in reporting adverse events and suspected product failures to help identify
potential problems as early as possible. The CVM recommends that veterinarians contact the drug company to report an ADE for their product and to ask to speak to a technical services veterinarian. Telephone numbers of drug companies can usually be obtained from product labeling. The technical services veterinarian should ask a series of questions about the event, complete the FDA 1932 form, and forward the report to the CVM. If the drug is not approved by the FDA, or if it is approved but the clinician does not want to contact the manufacturer, the ADE can be reported directly to the FDA on Form 1932a.

In summary, knowledge gained from ADE data is an important surveillance tool for continuous monitoring of drug safety and for veterinarians to learn about safety concerns that may not have been observed (or noticeable) during the drug approval process. However, the only way to maximize the ADE reporting value is through a concerted effort and commitment from practitioners, animal owners, manufacturers, and regulators to collect and report good-quality data that can be further analyzed and assessed for potential safety risks.

SUMMARY

Small animal practitioners have a variety of pharmacologic options in selecting the optimal treatment for their patients. However, the level of confidence in selecting the best treatment depends on the quality of information available to the practitioner on the safe and effective use of drugs. Understanding the differences between FDA-approved versus unapproved drugs and approved versus unapproved uses helps practitioners in making the right treatment decisions. Only when buying FDA-approved animal drugs are clinicians assured of the product safety, effectiveness, and manufacturing to the strict standards for quality, purity, and potency, and that the labeling is truthful and complete. It is critical for practitioners in modern veterinary practice to not only use drug labels and understand how they may affect their patients, but also to check them periodically for updates on important safety information.

Finally, the CVM Web site, http://www.fda.gov/AnimalVeterinary/default.htm, contains a wealth of information for veterinarians, consumers, and other parties interested in animal and veterinary topics. The free e-mail alert service allows subscribers to receive important CVM news and information as it becomes available. In addition, the CVM has a Twitter account, http://www.twitter.com/FDAanimalhealth, which provides another way to receive up-to-date information regarding veterinary drugs and medicine. Regular CVM updates allow veterinarians to remain current on new approvals for animal drugs, updated drug safety and health information, development of new drugs, current science and research at the CVM, and many other topics relevant to veterinary practice.

REFERENCE