



September 2015

DRUG COMPOUNDING FOR ANIMALS

FDA Could Improve Oversight with Better Information and Guidance

On January 8, 2016, footnote 16 on page 13 was corrected to read as follows: “For example, Florida grants licenses to sterile compounders, but it does not issue a special license to a pharmacy that compounds only nonsterile products.”

GAO Highlights

Highlights of [GAO-15-671](#), a report to congressional committees

Why GAO Did This Study

Drug compounding for animals involves combining, mixing, or altering ingredients to create drugs tailored to the medical needs of individual animals. While states have primarily exercised responsibility for oversight of drug compounding, FDA is responsible for ensuring the safety and effectiveness of drugs marketed in the United States, including animal drugs. FDA regulations generally allow for drug compounding for animals from approved animal or human drugs but not from bulk active pharmaceutical ingredients—the raw ingredients that make up finished drug products. Mistakes in compounding drugs for animals can result in injuries to or deaths of animals.

GAO was asked to review drug compounding for animals. This report examines (1) the benefits and risks of drug compounding for animals, (2) the extent of drug compounding for animals, and (3) FDA's approach to regulating these drugs. GAO reviewed federal regulations and guidance, FDA documents, and 18 peer-reviewed and other studies assessing drugs compounded for animals. GAO also interviewed federal and state regulatory officials, and a range of stakeholders in the animal health industry.

What GAO Recommends

GAO recommends that FDA modify its reporting form, develop guidance for agency staff regulating compounding for animals, and document consistently the bases for its regulatory actions. FDA generally agreed with GAO's recommendations.

View [GAO-15-671](#). For more information, contact Steve D. Morris at (202) 512-3841 or morris@gao.gov.

September 2015

DRUG COMPOUNDING FOR ANIMALS

FDA Could Improve Oversight with Better Information and Guidance

What GAO Found

Drugs compounded for animals offer certain medical benefits but also pose risks of causing harm or being ineffective. Specifically, drugs compounded for animals can serve as treatment options when no suitable drug approved by the Food and Drug Administration (FDA) is available. For example, no FDA-approved drugs exist to treat megacolon—a potentially lethal form of constipation—in cats, so veterinarians rely on a compounded drug for treatment. Drugs compounded for animals can also pose risks of serious harm or may be ineffective if they contain too much or too little of an active ingredient, according to scientific studies and veterinary experts. However, FDA has acknowledged that it is not practical for the agency to approve each drug compounded for every animal that requires one; as a result these drugs are not reviewed for safety and effectiveness. In addition, because states have primarily exercised responsibility for pharmacies that compound drugs for animals, the states and not FDA generally review pharmacy compounding processes.

The extent to which drugs are compounded for animals is unknown because the information FDA and states collect is not aggregated or comprehensive for various reasons. First, unlike animal drug manufacturers, drug compounding pharmacies do not have to register with FDA. Second, although FDA and states try to share information about drug compounding pharmacies with each other, due to some states' privacy and confidentiality laws this information sharing is impacted. For example, FDA officials told GAO that some states are unable to share information about the results of their pharmacy inspections with FDA because of their states' privacy laws. Finally, FDA does not know the extent to which compounded drugs are associated with adverse events, in part because the form used to voluntarily report such events does not ask if a compounded drug was involved. Federal standards for internal control state that agencies are to obtain information from stakeholders that may have a significant impact on achieving its goals. By not asking for compounded drug information on its reporting form, FDA is missing an opportunity to inform its enforcement actions regarding animal drug compounding.

FDA does not currently have final guidance directing its regulatory approach on drug compounding for animals and has not consistently documented the bases for the actions it has taken to regulate such compounding in the past. Until May 2015, FDA had guidance to direct its regulation of drug compounding for animals. In May 2015, FDA withdrew the guidance because it did not reflect FDA's current thinking on the issues and has not yet replaced it. This lack of guidance is inconsistent with federal internal control standards and raises concerns as to how FDA staff will make consistent decisions on enforcing animal drug compounding regulations in the future. Moreover, with regard to the actions FDA has taken against pharmacies compounding drugs for animals from bulk active pharmaceutical ingredients, the agency has not consistently documented how or whether it followed up on these actions. This lack of consistent documentation is also not in accordance with federal internal control standards, and without complete and consistent documentation of its actions, FDA cannot ensure that its regulatory approach is being applied consistently.

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Figure 1: Veterinarians Administer Compounded Drugs to Exotic Animals

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Abbreviations

ANADA	Abbreviated New Animal Drug Application
FDA	Food and Drug Administration
NADA	New Animal Drug Application

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September 28, 2015

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Fred Upton
Chairman
The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

Compounding drugs for animals, much like compounding drugs for humans, is the process of combining, mixing, or altering ingredients to create a drug tailored to the medical needs of an individual animal. Adverse events linked to drugs compounded for animals include the deaths of 21 polo horses given a performance-enhancing drug compounded by a Florida pharmacy in 2009.¹ More recently, in 2014 compounded drugs intended to treat equine protozoal myeloencephalitis—a serious disease affecting the central nervous

¹An adverse drug experience is any adverse event associated with the use of a new animal drug, whether or not considered to be drug related, and whether or not the new animal drug was used in accordance with the approved labeling (i.e., used according to label directions or used in an extralabel manner, including but not limited to different route of administration, different species, different indications, or other than labeled dosage). 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 C.F.R. § 514.3

system of horses—were produced at a pharmacy in Kentucky that resulted in the deaths of 4 horses and injuries to 6 others.²

Compounding is a traditional component of the practice of pharmacy. Pharmacies sometimes compound drugs for animals, usually upon receiving a prescription from a veterinarian. Some pharmacies compound only animal drugs, while others also compound human drugs. Veterinarians sometimes compound drugs for the animals they treat, using their own supplies of approved drugs and bulk drug substances.

Drug compounding is overseen at both the federal and state level. At the federal level, the Food and Drug Administration (FDA) within the Department of Health and Human Services is responsible for ensuring the safety and effectiveness of drugs marketed in the United States, including drugs intended for animals. Under the Federal Food, Drug, and Cosmetic Act and its implementing regulations, FDA approves new animal drugs and regulates their manufacture, marketing, and distribution. Drugs compounded from bulk drug substances for animals are considered new animal drugs under the act. However, the process of both animal and human drug compounding is also considered to be a pharmacy practice, which has traditionally been regulated by state pharmacy regulatory bodies (generally, boards of pharmacy), through state laws and regulations.³

In 2012, concerns were raised over this overlapping federal and state oversight of the practice of drug compounding for humans when an outbreak of fungal meningitis that killed more than 60 people and sickened hundreds of others was linked to contaminated compounded steroid injections. Although Congress subsequently passed the Drug Quality and Security Act in 2013, which provided for additional authorities with respect to drug compounding for humans, the legislation did not apply to drug compounding for animals. You therefore asked us to review issues related to drug compounding for animals and FDA's oversight.

²The drug was intended to treat equine protozoal myeloencephalitis, which is a serious disease of horses caused by a parasite spread through contaminated feed or drinking water. The disease causes lasting neurological damage.

³State pharmacy compounding regulations may also be enforced by state veterinary medicine boards. According to the *Journal of the American Veterinary Medical Association*, veterinarians have historically compounded drugs for in-office administration to animal patients or for dispensing to the owners of the animals.

This report examines (1) the benefits and risks of drugs compounded for animals, (2) the extent of drug compounding for animals, and (3) FDA's approach to regulating such compounding.

To address these objectives, we reviewed relevant federal law, regulations, and FDA guidance documents relevant to drug compounding for animals from bulk active pharmaceutical ingredients. To understand FDA activities, goals, and objectives related to oversight of compounding, we reviewed the FDA Foods and Veterinary Medicine Program Strategic Plan 2012-2016. We reviewed and analyzed other relevant FDA documents also, such as summary data and records of FDA regulatory activities, including documentation of compounding pharmacy inspections from 2002 to 2014 and reports of adverse events associated with veterinary drugs from 2001 to 2014. We compared FDA's guidance regarding compounding drugs for animals, which FDA withdrew during the course of our review in May 2015, and documentation of actions FDA has taken against pharmacies compounding drugs for animals from bulk active pharmaceutical ingredients with relevant standards of internal control for the federal government,⁴ and Office of Management and Budget instructions for drafting appropriate regulatory guidance.⁵ To assess the reliability of FDA's data, we interviewed FDA officials familiar with agency data systems and procedures for gathering, entering, and verifying data on actions FDA has taken against these compounding pharmacies, and adverse drug events, and reviewed agency documentation and guidance supporting data collection activities. We determined the data were sufficiently reliable for the purposes of determining FDA's actions to enforce regulations on drug compounding for animals. We also interviewed officials from FDA's Center for Veterinary Medicine, Center for Drug Evaluation and Research, and Office of Regulatory Affairs, including four district offices responsible for regulatory oversight in four states we selected for in-depth review. We selected these states—California, Florida, Kentucky, and Texas—because they vary in how they regulate compounding, are geographically dispersed, and two of them (Kentucky and Florida) have been the site of adverse events linked to drugs compounded for animals within the last 6

⁴GAO, *Standards of Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: November 1999).

⁵Office of Management and Budget, OMB Memorandum, M-07-07, *Final Bulletin for Agency Good Guidance Practices* (Washington, D.C.: 2007).

years, the period during which the most recent serious adverse events occurred.

For the four states, we reviewed relevant state statutes and regulations concerning compounding and interviewed animal health officials, specifically, officials of boards of pharmacy and veterinary medicine and veterinary medical associations, and supervising pharmacists. We also interviewed such officials involved with horse racing in Kentucky and Florida because, according to animal health officials we interviewed, racehorses often receive compounded drugs. The information we obtained from these states is not generalizable, but it furthered our understanding of key issues involved in drug compounding for animals. In addition, we conducted a literature search of peer-reviewed and other scientific studies assessing the quality of some compounded drugs and analyzed the results of these studies. We selected these studies by searching electronic databases of scientific journals for relevant articles published from 2003 to 2014 in which the quality or effectiveness of compounded animal drugs was identified as a key feature and also based on suggestions from experts in veterinary pharmacology identified by the American Veterinary Medical Association, a nonprofit organization representing more than 86,000 veterinarians nationally, and the Animal Health Institute, a trade organization representing manufacturers of animal drugs. Two GAO scientists with expertise in chemistry and biology reviewed each study we selected to confirm its methodological and scientific soundness. Finally, we interviewed a wide range of national stakeholders in the animal health industry, including veterinary pharmacology experts and representatives of trade organizations for drug manufacturers, pharmacists, and national veterinary associations specializing in equine and zoo animals. We identified these organizations in part from referrals by the American Veterinary Medical Association; the Pew Charitable Trusts, a nonpartisan, nongovernmental organization dedicated to informing public policy development; and the Animal Health Institute. For a more detailed discussion of the objectives, scope, and methodology for our audit, see appendix I. A list of the 18 studies we reviewed can be found in appendix II.

We conducted this performance audit from June 2014 to September 2015 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Compounding can involve manipulating an FDA-approved drug formulation for use in a manner that is not provided for in the drug's label directions. For example, compounding can entail combining two or more FDA-approved drugs or adding a nondrug component—such as flavoring—to an approved drug. Alternatively, compounding can involve formulating a drug from raw ingredients, which include bulk active pharmaceutical ingredients (also called bulk drugs) and inactive substances, such as fillers, or binders.⁶

Drugs compounded for animals from bulk active pharmaceutical ingredients are considered “new animal drugs” under the Federal Food, Drug, and Cosmetic Act. Before a new animal drug can be marketed under the act, it must be reviewed and approved or indexed by FDA for safety and effectiveness.⁷ Animal drugs that are not approved or indexed are considered unsafe and therefore adulterated under the act. According to FDA officials and documents, the agency's premarket review is integral to its ability to protect public health. During the premarket review, the agency evaluates information submitted by drug companies to determine whether a drug is safe and effective for its intended use and that the drug is properly manufactured and properly labeled. According to drug manufacturers, this review process can be costly for drug companies and take many years. In addition, after FDA approves the drug, the agency oversees the ongoing manufacture of the drug to determine that it is

⁶Bulk active pharmaceutical ingredients are active pharmaceutical ingredients generally sold and purchased in large quantities in pure (raw) form for use as key components in a finished drug product. FDA defines a bulk drug substance as any substance that is represented for use in a drug and that when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. In this report, to avoid confusion, we instead use the term bulk active pharmaceutical ingredients.

⁷Marketing is the process or technique of promoting, selling, and distributing a product or service. An indexed drug is a legally marketed unapproved new animal drug intended for use in minor species that has had safety and effectiveness affirmed through an alternative FDA review process. According to FDA, in many cases, minor species drug products are intended for uses that cannot reasonably go through the standard drug approval process. They are often intended for use in species too rare or varied to be used in traditional safety and effectiveness studies.

produced in accordance with Current Good Manufacturing Practices requirements, which help ensure the quality of drugs.⁸

⁸FDA enforces regulations called Current Good Manufacturing Practices. According to FDA, these regulations require proper design, monitoring, and control of manufacturing processes and facilities, including the use of strong quality management systems, appropriate quality raw materials, robust operating procedures, and reliable testing laboratories, among other things.

How to Identify an FDA-Approved Animal Drug



Source Boehringer Ingelheim Vetmedica, Inc. | GAO-15-671
FDA-approved animal drugs will have a New Animal Drug Application (NADA) number, or for generic animal drugs, an Abbreviated New Animal Drug Application (ANADA) number, which may appear on the label, though neither is required. A compounded drug label may state that the drug is FDA “registered” or “listed,” or made in an FDA “registered,” “inspected,” or “approved” facility. None of these designations means that the drug is FDA approved, however. Most FDA-approved animal drugs are listed in a searchable online database (<http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/>) called the Green Book, published annually and updated monthly.

Although drugs compounded for animals are “new animal drugs” under the Federal Food, Drug, and Cosmetic Act, FDA has acknowledged that it is not practicable for pharmacies to complete and obtain approval for a new drug application each time a compounded drug is prepared for an individual patient, and a compounded drug may be required in cases where a failure to treat would result in animal suffering or death.⁹

The Animal Medicinal Drug Use Clarification Act of 1994 provides an exception that allows drug compounding under specific conditions for animals without FDA premarket review and approval. The act and its implementing regulations authorize drug compounding for animals from FDA-approved human or animal drugs based on a prescription from a veterinarian for veterinary purposes under the following conditions:¹⁰

- no approved new animal or human drug can appropriately treat the condition diagnosed when the drug is used as labeled in the available dosage form and concentration;
- the compounding is performed by a licensed pharmacist or veterinarian within the scope of a professional practice;
- adequate procedures and processes are followed to ensure safety and effectiveness of the compounded drug;
- the scale of the compounding activity is in line with the established need for compounded products; and
- all relevant state laws relating to drug compounding for animals are followed.

FDA regulations allow drug compounding for animals from FDA-approved human or animal drugs under these conditions, but the regulations also state that nothing in the regulation “shall be construed as permitting compounding from bulk drugs.”

⁹Drugs compounded for animals are not equivalent to generic animal drugs. Generic animal drugs, like new animal drugs, must be reviewed and approved by FDA before they are marketed to the public, and must comply with Current Good Manufacturing Practice requirements.

¹⁰21 U.S.C. § 360b(4)(a); 21 C.F.R. § 530.13.

Drugs Compounded for Animals Offer Benefits but May Pose Health Risks

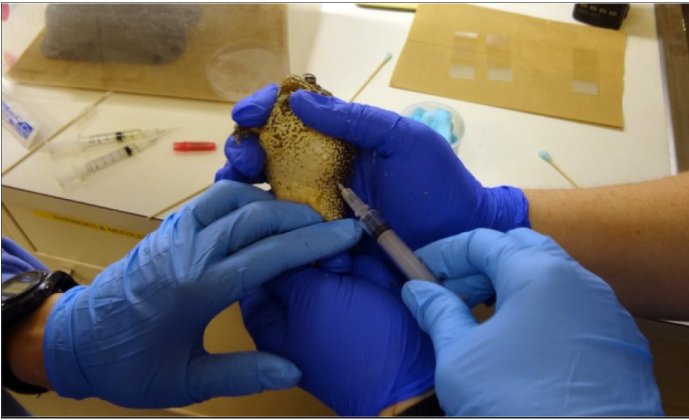
Drugs compounded for animals offer medical and other benefits but may pose a risk of causing serious harm or being ineffective.

Drugs Compounded for Animals Offer Medical and Other Benefits

Drugs compounded for animals offer benefits such as providing treatment options when no suitable FDA-approved drug is available. For example, there are no FDA-approved drugs to treat megacolon—a severe form of constipation—in cats, so veterinarians rely on compounded cisapride for treatment.¹¹ According to representatives of organizations representing compounding pharmacists and veterinarians, there are no substitutes for cisapride in cats, and many cats with megacolon would have to be euthanized without cisapride treatment. Drugs compounded for animals may also be more suitable than other treatment options because they allow for easier and more appropriate administration of medication to animals. For example, compounding a drug may consist of adding flavor (e.g., beef flavoring to a pain medication for arthritis) to increase its palatability or changing its form (e.g., creating a paste from a tablet) to provide a more convenient method of administering the medication and to improve absorption. The ability to tailor medications through compounding is especially important in treating exotic animals. Compounding allows veterinarians to accommodate the extensive diversity of sizes and features associated with exotic animals such as large mammals, reptiles, and birds. (For pictures of exotic animals receiving treatment with compounded drugs, see fig. 1.)

¹¹Cisapride approved for human use was voluntarily withdrawn from the U.S. market in 2000 because of severe adverse events including rare, but serious, heart rhythm disorders and several deaths. When drugs—including drugs for humans that are commonly used to treat animals—are removed from the market, veterinarians rely on compounded drugs if there is no other approved drug available.

Figure 1: Veterinarians Administer Compounded Drugs to Exotic Animals



Sources: Houston Zoo (left); L. Penfold (right). | GAO-15-671

This Houston Toad (above) is receiving an injected hormone treatment in a captive breeding and release program. According to a veterinarian at the Houston Zoo, some endangered exotic animals, like the Houston Toad pictured above, would be extinct if compounded drugs and hormones were not available to keep them healthy and propagate them.

Veterinarians are inserting an endotracheal tube into an anesthetized elephant. According to an association representing zoo veterinarians, humans and animals could be seriously injured if large animals, like the elephant pictured above, are not properly anesthetized with compounded specialized drugs.

Compounded drugs also may provide treatment at lower cost than FDA-approved drugs. The American Veterinary Medical Association, a professional organization of veterinarians, and the FDA have both stated that cost is not an appropriate reason to use compounded drugs instead of FDA-approved drugs, however. For example, some animal owners are unable or unwilling to buy an expensive FDA-approved drug, and a veterinarian may prescribe a lower priced drug compounded from bulk active pharmaceutical ingredients to alleviate suffering or save an animal that might otherwise die. One veterinarian told us that veterinarians have prescribed a compounded drug for chemotherapy because such drugs are often prohibitively expensive for pet owners. According to the American Veterinary Medical Association, animals are rarely covered by health insurance. Because animal owners generally pay for animal drugs out of pocket, the availability of less costly drugs can be important to some animal owners, according to some veterinarians we interviewed.

Drugs Compounded for Animals May Pose Risks of Serious Harm or Be Ineffective

Drugs compounded for animals may pose risks of serious harm or may be ineffective for two reasons, according to FDA officials. First, FDA generally does not review drugs compounded for animals for safety and effectiveness because, according to agency officials, it is not practical for FDA to approve each drug compounded for every animal that requires

one. Second, because states have primarily exercised responsibility for pharmacies, according to agency officials, FDA does not generally oversee the compounding process for quality manufacturing practices.

FDA's position that drugs compounded for animals may cause serious harm or be ineffective is consistent with findings from published scientific studies we reviewed, as well as with the views of veterinary pharmacology experts we interviewed. According to these scientific studies and veterinary pharmacology experts, some drugs compounded for animals may contain too much or too little of an active ingredient and, as a result, may be either toxic or ineffective. For example, a batch of ingredients that is not uniformly distributed could produce compounded tablets with different levels of the active ingredient. A 2011 study of clenbuterol, a drug intended to dilate the bronchial airways in horses to ease breathing, found that a compounded formulation of this drug contained 70 times the concentration of the FDA-approved drug and likely led to deaths of 2 horses and adverse reactions in 11 others.¹² We reviewed four other studies that tested the accuracy of compounded drugs by comparing the drugs' actual characteristics to the specifications on their labels.¹³ These studies found that the compounded drugs tested generally did not meet specifications.

In a broader assessment carried out annually by the Missouri Board of Pharmacy, about one-fifth of randomly selected compounded drugs obtained from licensed state pharmacies from 2006 through 2014 were found to contain substantially less or more (from 0 percent to 450

¹²J.A. Thompson, M.H. Mirza, S.A. Barker, T.W. Morgan, R.W. Bauer, and R.S. McConnico, "Clenbuterol Toxicosis in Three Quarter Horse Racehorses after Administration of a Compounded Product," *Journal of the American Veterinary Medical Association*, vol. 239, no. 6 (2011).

¹³A.K. Cook, C.D. Nieuwoudt, and S.L. Longhofer, "Pharmaceutical Evaluation of Compounded Trilostane Products," *Journal of the American Animal Hospital Association*, vol. 4, no. 8 (2012); M.E. Umstead, D.M. Boothe, C. Cruz-Espindola, J.M. Macdonald, R. Kennis, and D. Angarano, "Accuracy and Precision of Compounded Ciclosporin Capsules and Solution," *Veterinary Dermatology*, vol. 23, no. 431 (2012); J.C. Scott-Moncrief, G.E. Moore, J. Coe, R.C. Lynn, W. Gwin, and R. Petzold, "Characteristics of Commercially Manufactured and Compounded Protamine Zinc Insulin," *Journal of the American Veterinary Medical Association* vol. 240, no. 5 (2012); S.D. Stanley, S.M. Thomas, and W. Skinner, "Comparison for Pharmaceutical Equivalence of FDA-Approved Products and Compounded Preparations of Ketoprofen, Amikacin, and Boldenone," *American Association of Equine Practitioners* (International Veterinary Information Service: Ithaca, NY: 2003)

percent) of the active ingredient than stated on the drug's label.¹⁴ We also reviewed 10 studies comparing reference drugs to drugs that were compounded to allow a different route of administration. These studies all found that the compounded drugs with an alternate route of administration were poorly absorbed, decreasing the likelihood that the drugs would be effective in clinical situations. In two additional studies, compounded drugs also exhibited poor absorption even though they had the same route of administration as the reference drugs. (For a list of studies we reviewed, see app. II.)

In addition, according to veterinarians we interviewed, because drugs compounded for animals are not tested by FDA and may not list side effects on their labels, they may cause side effects that pose risks to humans administering these drugs. For example, compounded drugs may cause unforeseen side effects, including sporadic behavior, such as kicking in large animals, placing humans at risk. They may also cause side effects if the drugs contact human skin. To illustrate, a drug sometimes compounded to control estrus (i.e., ovulation) in horses has the potential to cause pregnant women who administer it to miscarry, according to a veterinarian we interviewed.

Representatives we interviewed from pharmacies that specialize in veterinary drugs said that, except for emergency prescriptions, they routinely test all the drugs they compound to ensure the appropriate ingredients are in the right proportions. However, they also said that not all compounding pharmacists test their drugs and that there is no legal requirement to do so.

¹⁴Missouri Board of Pharmacy, *Annual Report* (Jefferson City, MO: 2006-2014). The compounded drugs tested were listed by name but were not identified as human or animal drugs. According to FDA, the drug names included some active pharmaceutical ingredients tested that are approved in both FDA human and animal drug applications.

The Extent to Which Drugs Are Compounded for Animals and Involved in Adverse Events Is Unknown

The extent to which drugs are compounded for animals is unknown because the information that FDA and states collect on drug compounding is not aggregated or comprehensive. FDA maintains information on pharmacies it has inspected for potentially violating compounding regulations, but states are the primary holders of information on pharmacies. Unlike animal drug manufacturers, which are required to register with FDA, pharmacies—including those compounding animal drugs—are not required to register with FDA.

States license pharmacies to practice in their borders and maintain certain information on pharmacy operations. For example, pharmacy representatives we interviewed in the four states we reviewed told us that state pharmacy boards keep records of pharmacy ownership, location, inspections, and regulatory noncompliance—information that if aggregated and analyzed might shed some light on the extent to which drugs are compounded for animals. Both FDA and state pharmacy officials we interviewed said they try to share information to the extent possible, including information collected during inspections where both FDA and state officials are present. FDA can also share some information with state pharmacy officials who have provided a written statement of authority to protect confidential commercial information from public disclosure and provide a written commitment to do so, or by commissioning state pharmacy board officials as FDA representatives.¹⁵

Even with these agreements, however, FDA and state officials said that they might decline to share documentation useful for oversight purposes if they considered it to be confidential or personal. For example, FDA will not share such information with Florida state officials because the agency is required under federal law to safeguard such information from public disclosure, and Florida's open records law requires regulatory officials to make information broadly available for public review. FDA officials said that some states also have privacy and confidentiality laws that restrict pharmacy officials from sharing inspection information with FDA. Moreover, even if FDA were able to collect information on pharmacies

¹⁵FDA can share confidential commercial information and information concerning the deliberative process involved in an FDA inspection with state government officials under what is commonly called a "20.88" agreement. The conditions and requirements for sharing such information can be found in section 20.88 of title 21 to the *Code of Federal Regulations*. According to FDA officials, the agency can share personal privacy information under such an agreement but does not do so routinely because of the sensitive nature of the information.

from all 50 states, states do not always distinguish between compounding pharmacies and pharmacies that do not compound, or, according to FDA, among pharmacies that compound only human drugs, only animal drugs, or both human and animal drugs. As a result, aggregated information from states would not necessarily help FDA determine the extent of drug compounding for animals. Two of the four states we reviewed did not make a distinction between pharmacies that compound drugs in general and pharmacies that do not compound, according to state officials we interviewed.¹⁶

FDA also does not know the extent to which compounded drugs may have caused or been linked to adverse events, in part because it does not specifically solicit such information. To obtain information on adverse events reports, FDA relies on voluntary reporting from veterinarians and pet owners, as well as from pharmacies. Regulations require that drug manufacturers report adverse events associated with the drugs they produce, but regulations do not expressly require pharmacies to report adverse events associated with the compounded drugs they prepare. According to FDA documents, since 2001, the agency has received 62 voluntary reports of adverse events identified as being associated with drugs compounded for animals. However, this number likely does not represent the actual number of adverse events related to drugs compounded for animals, in part because the reporting form FDA uses in collecting information on adverse events does not specifically solicit information on whether the drugs involved in the events were compounded. (For a copy of FDA's voluntary adverse event reporting form, see app. III.)

According to FDA officials, incomplete information in adverse events reporting forms makes it difficult for the agency to determine whether the drug involved was compounded and how often such adverse events actually occurred. Federal standards for internal control call for agencies to ensure that there are adequate means of obtaining information from external stakeholders that may have a significant impact on the agency achieving its goals.¹⁷ By not specifically asking, on its voluntary reporting form, whether drugs involved in adverse events were compounded, FDA

¹⁶For example, Florida grants licenses to sterile compounders, but it does not issue a special license to a pharmacy that compounds only nonsterile products.

¹⁷[GAO/AIMD-00-21.3.1](#).

is missing an opportunity to gather information that could help inform its future actions taken against pharmacies for compounding drugs for animals from bulk active pharmaceutical ingredients. Agency officials told us that amending FDA's voluntary reporting form to request this type of information would not be difficult and agreed that it could provide valuable information. Such information, for example, could potentially help FDA identify compounding practices or specific compounded drugs that may pose increased risks and that the agency could use to help target its regulatory efforts accordingly.

FDA Does Not Have Guidance on Its Approach to Regulating Drug Compounding for Animals, and the Bases for Its Decisions Are Not Consistently Documented

Until recently, FDA had guidance to direct its regulation of drug compounding for animals, but the agency no longer has such guidance because it withdrew it in May 2015 and has not issued new final guidance. In addition, the agency has not consistently documented the bases for the actions it has taken in the past against pharmacies compounding drugs for animals from bulk active pharmaceutical ingredients.

FDA Does Not Have Guidance for Its Regulation of Drug Compounding for Animals from Bulk Active Pharmaceutical Ingredients

Until May 2015, FDA articulated its regulatory approach in a 2003 compliance policy guide the agency had issued to describe what factors the agency would consider in taking action for drug compounding for animals.¹⁸ The guide stated that drug compounding for animals from bulk active pharmaceutical ingredients violates the Federal Food, Drug, and Cosmetic Act, but the guide also stated that FDA would seriously consider taking action when the scope and nature of the activities of veterinarians and pharmacists raised concerns normally associated with drug manufacturing or resulted in significant violations of the act.

We reviewed the guide and noted that it contained several limitations, including terms that were not defined. We discussed our observations several times with FDA officials from July 2014 to March 2015. These officials pointed out the weaknesses in the guide and requirements for compounding. It is our conclusion, based on discussions with FDA officials, that they agree that the guide needed revision. For example, the guide stated that FDA would consider taking action if drugs are compounded using “commercial scale manufacturing equipment,” but did not define “commercial scale.” The guide also stated that FDA would not take action if drugs were compounded in anticipation of receiving prescriptions except in “very limited quantities,” but did not define what was meant by “very limited.” The use of such terms without clear explanation in the compliance policy guide caused confusion among stakeholders, a situation that makes compliance and enforcement difficult.

In May 2015, FDA withdrew its compliance policy guide leaving agency staff with no guidance for regulating drug compounding for animals from bulk active pharmaceutical ingredients. Prior to its withdrawal, compliance staff relied primarily on the guide when determining whether the agency would take action, according to FDA officials. A May 2015 *Federal Register* notice stated that FDA withdrew the guide because it is no longer consistent with the agency’s current thinking on the issues.¹⁹

¹⁸Food and Drug Administration, *Guidance for FDA Staff and Industry: Compliance Policy Guides Manual, Sec. 608.400, Compounding of Drugs for Use in Animals* (July 2003).

¹⁹80 *Fed. Reg.* 28624 (May 19, 2015). Specifically, FDA stated that the withdrawn guide did not focus on the three main concerns FDA has about animal drug compounding: compounding copies of approved animal or human drugs from bulk active pharmaceutical ingredients, compounding for food-producing animals from bulk active pharmaceutical ingredients, and compounding office stock from bulk active pharmaceutical ingredients.

Under federal standards of internal control, agencies are to clearly document internal controls, and the documentation is to appear in management directives, administrative policies, or operating manuals.²⁰ Without documented policy or guidance, FDA staff do not have clear direction on which to base their decisions about whether and how to enforce regulations on drug compounding for animals, raising questions as to how staff can consistently enforce such regulations. In particular, this will become more important as the draft industry guidance discussed below becomes final.

FDA Has Proposed Guidance for Industry and Made It Available for Public Comment

As FDA withdrew its 2003 compliance policy guide, the agency also announced the availability of draft guidance for industry on drug compounding for animals from bulk active pharmaceutical ingredients. The *Federal Register* notice stated that the draft guidance, when final, would represent FDA's current thinking on the issues. Similar to the agency's 2003 compliance policy guide, the agency's draft guidance underscores that drug compounding for animals from bulk active pharmaceutical ingredients violates federal law but acknowledges that compounded drugs may sometimes be an appropriate treatment option when no FDA-approved drug is available.²¹

Accordingly, the draft guidance describes conditions under which FDA will generally not take enforcement actions for violations of specific provisions of the Federal Food, Drug, and Cosmetic Act. Animal drugs are generally subject to the adulteration, misbranding, and approval provisions of the act. However, generally, FDA does not intend to take action for certain listed violations of the act if the conditions set out in the draft guidance are met. (App. IV provides a complete list of the conditions in FDA's draft, as of May 2015, under which the agency generally does not intend to take action to enforce restrictions on drug compounding for animals from bulk active pharmaceutical ingredients.)

²⁰[GAO/AIMD-00-21.3.1](#).

²¹Food and Drug Administration, *Guidance for Industry No. 230: Compounding Animal Drugs from Bulk Drug Substances (Draft Guidance)* (Washington, D.C.: May 2015).

This draft guidance includes specific lists of conditions that should be met by pharmacies, veterinarians, and outsourcing facilities.²² For example, in the case of pharmacies, the drug should be compounded by, or under the direct supervision of, a licensed pharmacist; in the case of veterinarians, the drug should be compounded and dispensed by a licensed veterinarian to treat an individually identified patient under his or her care. In addition, the prescription for a drug compounded by a pharmacist should include a statement from a prescribing veterinarian stating that there is no approved animal or human drug that can appropriately treat the disease, symptom, or condition. According to the *Federal Register* notice on the draft guidance, this guidance provides information to compounders of animal drugs and other interested stakeholders on FDA's application of the Federal Food, Drug, and Cosmetic Act with respect to the compounding of animal drugs from bulk active pharmaceutical ingredients.

FDA Has Taken Actions against Compounding Pharmacies but Has Not Consistently Documented the Bases for These Actions

Since fiscal year 2003, FDA has taken various actions against pharmacies compounding animal drugs from bulk active pharmaceutical ingredients, including conducting inspections and issuing warning letters, to address potential problems regarding drug compounding for animals, but has not consistently documented the bases for these actions.

FDA Has Conducted Inspections, Issued Warning Letters, and Taken Enforcement Actions

Actions FDA may take against compounding pharmacies include inspections, warning letters, seizures, injunctions, and criminal prosecution. An inspection of a pharmacy typically involves examining, among other things, the condition of the facility, and a review of the types of drugs compounded, controls for sterile compounding, training records,

²²In 2013, Congress enacted the Drug Quality and Security Act. This act amended the Federal Food, Drug, and Cosmetic Act to provide for "outsourcing facilities." Outsourcing facilities are facilities that compound sterile drugs and agree to register with FDA. The act allows these facilities to compound drugs using listed bulk active pharmaceutical ingredients if the facilities comply with a number of restrictions and requirements. According to FDA officials, the act applies only to drug compounding for humans. However, because pharmacies can compound drugs for both humans and animals at the same facility, drugs compounded for animals at such pharmacies are also subject to the requirements.

employee practices, complaints, and laboratory testing records. According to FDA officials, the agency does not routinely inspect pharmacies that compound drugs for three primary reasons:

- FDA does not have a comprehensive list of such pharmacies because they are not required to register with the agency;
- FDA does not have the resources to routinely inspect the thousands of pharmacies and veterinarians that compound drugs for animals, even if such pharmacies were registered with the agency; and
- states regulate pharmacy practice and drug compounding.

However, FDA officials said the agency has conducted inspections of compounding pharmacies in response to adverse events or complaints about illegal compounding, called “for cause” inspections.²³ Since fiscal year 2003, FDA has carried out 39 inspections in response to complaints related to drug compounding for animals, including multiple inspections at some pharmacies. FDA officials said that, depending on the results of an inspection, the agency may take several actions, including (1) issuing a warning letter telling a pharmacy it has violated the law and should take corrective action and (2) requesting a voluntary recall of a potentially unsafe compound.²⁴ If these actions prove ineffective, or the identified violations are particularly egregious, FDA officials said they have the authority to take legal action, such as obtaining an injunction to stop a pharmacy from operating. As a result of violations identified during those inspections conducted since 2003, the agency has issued 15 warning

²³According to FDA officials, the agency received approximately \$2 million in additional funding in fiscal year 2015 to address drug compounding for animals. With the increased funding, FDA plans to, among other things, develop and implement a surveillance program involving sampling and analysis of purchased compounded products to identify pharmacies that compound drugs for animals to conduct inspections based on risk assessment.

²⁴FDA’s authority to require companies to recall a product does not apply to drugs, including drugs compounded for animals. As such, all recalls of drugs compounded for animals are voluntary, according to FDA officials. FDA also issues notifications about potential issues with drugs compounded for animals, which can be found at <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/ucm417562.htm>.

letters to pharmacies, worked to have pharmacies issue three voluntary recalls, and taken four legal actions against pharmacies.²⁵

FDA issued warning letters to compounding pharmacies and veterinarians for a variety of reasons, including compounding from bulk active pharmaceutical ingredients in a quantity associated with manufacturing and compounding with no documented medical need. FDA officials said, however, that the agency has not pursued a legal action to stop a pharmacy from illegally compounding drugs for animals since 2010, when the agency sought an injunction against a Florida-based pharmacy. According to FDA's legal complaint, FDA inspected the pharmacy following deaths of 21 polo horses that died after receiving a compounded drug from the pharmacy. During subsequent inspections, FDA observed violations of federal law at the pharmacy and informed the pharmacy of the violations. The pharmacy responded that its actions were not subject to FDA's new animal drug manufacturing authority. FDA then sought an injunction in federal district court to stop the pharmacy from distributing animal drugs compounded from bulk active pharmaceutical ingredients. The pharmacy challenged the injunction on grounds that the agency did not have the authority to regulate pharmacy compounding for nonfood-producing animals because, among other things, Congress had recognized when enacting the Federal Food, Drug, and Cosmetic Act that traditional pharmacy practices were closely regulated by state authorities. The district court subsequently found in favor of the pharmacy. That decision was vacated as moot on appeal by joint motion of the parties, however, because the defendants stopped compounding animal drugs from bulk active pharmaceutical ingredients.

FDA officials said compounding pharmacies have brought such challenges to FDA's authority to regulate drugs compounded for animals on several occasions, resulting in legal reviews and appeals, but the courts have generally ruled in FDA's favor. (App. V provides examples of legal challenges to FDA's authority.) Even though historically FDA has prevailed in some animal drug compounding cases, officials said that the continued challenges to FDA's authority have led the agency to carefully consider which actions to pursue. FDA officials indicated these considerations include the resources that are required, as well as how

²⁵FDA also requested eight other voluntary recalls that involved drugs compounded for animals. We did not include those recalls in this count because they were initiated in response to inspections related to issues with drug compounding for humans.

flagrant the violations are and how significant the threat is to animal and public health. FDA officials stated that decisions favorable to FDA in the past do not guarantee that future challenges to FDA's regulatory authority will result in the courts affirming this authority.

Representatives of animal drug manufacturers and a manufacturers' trade organization we interviewed told us FDA does not seem to be taking much enforcement action despite the proliferation of drugs compounded for animals, which encourages compounding pharmacies to circumvent FDA's drug approval process and may discourage manufacturers from developing new drugs. Moreover, according to these representatives, some pharmacies have moved beyond compounding based on a prescription for an individual animal to producing large quantities of compounded drugs from bulk active pharmaceutical ingredients without prescriptions—and sometimes providing these drugs when there is no medical need for them. These drugs are often sold at a lower cost than FDA-approved drugs, the representatives said.

Animal health industry representatives we interviewed said that a compounded product—when compounded from FDA-approved drugs in accordance with FDA regulations—should be more expensive than an unaltered FDA-approved drug because the cost of other ingredients (e.g., flavoring) and the cost of labor to alter the drug typically make the price higher. The representatives said that pharmacies selling compounded versions of FDA-approved drugs at a lower cost likely compounded the drug from bulk active pharmaceutical ingredients, which violates the law.

FDA officials we interviewed told us they have worked to curtail similar illegal activity that compromises the integrity of the drug approval process. For example, 14 of the 15 warning letters FDA issued relating to drug compounding for animals since 2003 involved violations related to compounding from bulk active pharmaceutical ingredients or compounding when FDA-approved drugs were available. In one of these cases, FDA turned to the federal courts, getting the U.S. Marshals Service to seize the illegally compounded drugs. In two others, the pharmacies receiving the warning letters agreed to cease compounding from bulk active pharmaceutical ingredients or implement corrective action to address their violations.

FDA Has Not Consistently Documented the Bases for Its Actions against Compounding Pharmacies

FDA has not consistently documented the bases for its decisions about how or whether it followed up on warning letters, adverse event reports from the public, veterinarians, or pharmacies, or complaints about illegal compounding from manufacturers. FDA's follow-up to warning letters ranged from 9 months to years or no apparent follow-up at all. For example, in 2003, FDA issued a warning letter to a pharmacy after identifying several violations, including compounding on a scale associated with manufacturing, during an inspection of the facility. In that case, FDA was able to have compounded drugs seized—which can involve lengthy legal proceedings and coordination with other federal agencies—from the pharmacy within 9 months of issuing the letter. In contrast, FDA issued a warning letter to another pharmacy in 2006 after identifying a similar list of violations, but the agency did not take additional action at the pharmacy until 2012, 6 years later, after the death of a horse was associated with a different compounded drug from the pharmacy. Documentation that FDA provided does not indicate whether (1) the 2006 violations were resolved or (2) a connection exists between the 2006 and 2012 events. As a result, we could not determine the bases for the differences in the agency's follow-up activities to these warning letters.

Similarly, FDA's bases for its handling of adverse event reports was not always clearly documented. For example, FDA provided documentation showing that agency staff had inspected and issued one pharmacy a warning letter in response to certain adverse event reports, but the violations identified in the warning letter to the pharmacy did not reflect concerns raised or drugs used in the reported adverse events. In addition, FDA provided documentation indicating that one adverse event report linking a compounded drug to a horse death was referred to FDA's Office of Emergency Operations because the event involved a death.²⁶ But the documentation the agency provided did not indicate whether other adverse event reports involving animal deaths had been similarly forwarded to the emergency operations office. FDA officials said that other adverse event reports involving the death of an animal were most likely also forwarded to the office, but the agency could not provide documentation supporting this position. We were also unable to determine how FDA handles complaints about illegal compounding, which FDA typically receives by mail, e-mail, or telephone calls from drug

²⁶The Office of Emergency Operations provides support and assistance to FDA offices in managing the agency's response to emergency incidents and situations involving FDA regulated products.

manufacturers because the agency does not track or collect this information.²⁷ FDA officials told us that the agency has taken actions in response to such complaints, but that unlike adverse events reports, it does not track the number or types of complaints received or document how such complaints are ultimately addressed.

Under federal internal control standards, agencies are to employ control activities, such as appropriately documenting transactions and internal controls.²⁸ Such control activities would require, for example, FDA to consistently document the bases for taking action or not taking action to follow up on a warning letter, adverse event report, or complaint, as well as how each case was finally addressed. As long as FDA does not have documentation supporting its actions about drug compounding for animals, the agency cannot ensure that its regulatory approach is applied consistently. FDA officials we interviewed said that officials responsible for reviewing agency actions are expected to ensure that violations that are similar in nature receive consistent uniform responses from the agency. However, FDA officials also said compliance staff primarily relied on the 2003 compliance policy guide when determining whether the agency would take action. As previously mentioned, the guide did not clearly explain the conditions that warranted action and now that it has been withdrawn, staff have no guidance to follow to help ensure a consistent approach. The officials agreed that better documenting what actions have been taken and the reasons for them would help the agency ensure more consistency in regulating drug compounding for animals.

Conclusions

FDA approves new animal drugs and regulates their manufacture, marketing, and distribution, but drugs that are compounded for use in animals do not receive FDA review and approval. While drugs compounded for animals offer medical and other benefits, they also pose a risk of causing serious harm or being ineffective. To obtain information on adverse events, FDA relies on voluntary reporting by veterinarians and

²⁷Complaints about illegal compounding typically involve issues with a compounding pharmacy's operations in contrast to adverse event reports, which generally involve animal injuries resulting from treatment with a compounded drug. Complaints of illegal compounding include allegations such as compounding drugs for animals on the scale of a drug manufacturer or compounding copies of FDA-approved drugs from bulk active pharmaceutical ingredients.

²⁸[GAO/AIMD-00-21.3.1](#).

pet owners. However, the reporting form that FDA uses to gather such information does not ask whether the drug involved in an adverse event was compounded. By not specifically asking on its voluntary reporting form whether drugs involved in adverse events were compounded, FDA is missing an opportunity to gather information that could help inform its future actions against pharmacies compounding drugs for animals from bulk active pharmaceutical ingredients.

In addition, until May 2015, FDA had a compliance policy guide in effect that described how FDA intended to address compounding of animal drugs from bulk active pharmaceutical ingredients and the agency's current thinking on what types of compounding might be subject to enforcement action. FDA's guide had some limitations and FDA withdrew the guide in May 2015 because, according to its *Federal Register* notice, the guide was no longer consistent with the agency's current thinking on drug compounding for animals. With the withdrawal of the guide, FDA staff no longer have documented policy or guidance on which to base their decisions about whether and how to enforce regulations on drug compounding for animals, raising questions as to how staff can consistently enforce such regulations. This issue is of particular concern as the agency is in the process of developing new guidance for industry on drug compounding for animals.

Finally, when FDA has taken actions to address potential problems at pharmacies regarding drug compounding for animals, it has not consistently documented the bases for its decisions about how or whether it followed up on warning letters, adverse event reports from the public, veterinarians, and pharmacies, or complaints about illegal compounding from animal drug manufacturers. As long as FDA does not document the bases for its actions against pharmacies compounding drugs for animals from bulk active pharmaceutical ingredients, the agency cannot ensure that its regulatory approach is applied consistently.

Recommendations for Executive Action

To help ensure that FDA has relevant and timely information to support management decisions, including the critical information necessary to ensure the safety and effectiveness of drugs compounded for animals, we recommend that the Secretary of Health and Human Services direct the Commissioner of the FDA to take the following three actions:

- Modify the voluntary reporting form FDA uses to obtain information on adverse events to ask whether drugs involved in adverse events were compounded.

-
- Develop policy or guidance for agency staff that specifies circumstances under which FDA will or will not enforce compounding regulations for animals and clearly define key terms.
 - Consistently document the bases for FDA's decisions about how or whether it followed up on warning letters, adverse event reports, and complaints about drug compounding for animals.

Agency Comments

We provided a draft of this report to the Department of Health and Human Services for review and comment. The department transmitted written comments from FDA, reproduced in appendix VI, in which FDA generally agreed with our recommendations. FDA also stated that it has made substantial progress addressing animal drug compounding. In addition to withdrawing the outdated 2003 Compliance Policy Guide and publishing draft Guidance for Industry on compounding animal drugs from bulk active pharmaceutical ingredients, the agency stated that it has taken other steps, including hiring a compounding coordinator to oversee all veterinary compounding, as well as hiring additional veterinary, consumer safety, and regulatory staff to assist in matters related to animal drug compounding. FDA stated that it also has expanded the agency's webpage dedicated to animal and veterinary compliance and enforcement to include information on inspections, recalls, and other actions involving firms that compound animal drugs. FDA also provided technical comments that we incorporated, as appropriate.

We are sending copies of this report to the appropriate congressional committees, the Commissioner of the Food and Drug Administration, the Secretary of Health and Human Services, and other interested parties. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff members have any questions about this report, please contact me at (202) 512-3841 or morriss@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who make key contributions to this report are listed in appendix VII.



Steve D. Morris,
Director, Natural Resources and Environment

Appendix I: Objectives, Scope, and Methodology

This report examines (1) the benefits and risks of drug compounding for animals, (2) the extent of drug compounding for animals, and (3) the Food and Drug Administration's (FDA) approach to regulating such compounding.

To determine the benefits and risks of drugs compounded for animals and the extent of drug compounding for animals, we conducted a literature search of peer-reviewed and other scientific research assessing the quality of some compounded drugs and analyzed the results. We selected these studies by searching electronic databases of science journals for relevant articles published from 2003 to 2014 in which compounded animal drugs were addressed. We also identified studies based on suggestions from experts in veterinary pharmacology. These experts were identified by the American Veterinary Medical Association, a nonprofit organization representing more than 86,000 veterinarians in private and corporate practice, government, industry, academia, and the uniformed services, and the Animal Health Institute, a trade organization representing manufacturers of animal drugs. We also identified studies by looking at the references in these studies to find additional relevant studies for review. Two scientists with expertise in chemistry and biology reviewed each study used in our report to confirm its methodological and scientific soundness. (For a list of the research studies included in our review, see app. II.) We also interviewed pharmacology experts and pharmacy representatives knowledgeable about animal drugs, including authors of the peer-reviewed studies we analyzed, and representatives with the National Community Pharmacists Association, and the International Academy of Compounding Pharmacists. We identified organizations through their prior testimony before Congress on drugs compounding and based on recommendations of organizations knowledgeable about animal drugs compounding or pharmaceutical quality and safety, including the American Veterinary Medical Association, a nonprofit organization; and the Pew Charitable Trusts, a nonpartisan, nongovernmental organization dedicated to informing public policy development.

In addition, we interviewed a wide range of representatives of organizations involved with the nation's animal health industry. These organizations included trade organizations for drug manufacturers, such as the Generic Animal Drug Alliance and the Animal Health Institute. We also interviewed representatives of companies engaged in animal drugs manufacturing, such as Zoetis and Dechra. Both the trade organizations and company officials we interviewed were recommended to us by the Animal Health Institute or the American Veterinary Medical Association.

We also interviewed representatives of a variety of veterinary specialties, as well as selected state and national veterinary associations to better understand how compounded animal drugs are used and how widely they are used. These included representatives of the American Veterinary Medical Association and representatives of the American Association of Equine Practitioners and the American Association of Zoo Veterinarians. We selected the aforementioned national organizations in pharmacy and animal health from those identified as having an interest in animal drugs compounding or animal health by the American Veterinary Medical Association, and the Pew Charitable Trusts. We also interviewed officials with state veterinary organizations in California, Florida, Kentucky, and Texas. The state-level veterinary associations we interviewed were selected as part of a four-state review of the animal drugs oversight practices carried out by state authorities. We selected these states—California, Florida, Kentucky, and Texas—because they vary in how they regulate compounding, are geographically dispersed, and two of them (Kentucky and Florida) have been the site of adverse events linked to drugs compounded for animals within the last 6 years, the period during which the most recent serious adverse events occurred.

To determine FDA’s regulatory approach to drug compounding for animals, we reviewed relevant federal law, regulations, and guidance documents relevant to drug compounding for animals. To get a better understanding of the goals and objectives related to oversight of compounding, we reviewed the agency’s most recent strategic plans and strategic priorities.¹ We reviewed other relevant FDA documents also, such as summary data and records of FDA regulatory activities, including documentation of compounding pharmacy inspections and reports of adverse events associated with veterinary drugs. We compared FDA’s withdrawn 2003 compliance policy guide regarding compounding drugs for animals and documentation of FDA’s actions against pharmacies compounding drugs from bulk active pharmaceutical ingredients with the standards of internal control for the federal government and Office of Management and Budget instructions for drafting appropriate regulatory

¹Food and Drug Administration, Office of Foods, Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, Office of Regulatory Affairs, *FDA Foods and Veterinary Medicine Program, Strategic Plan 2012-2016* (Washington, D.C.: April 2012) ; *FDA Strategic Priorities 2014-2018*, (Washington, D.C.: undated).

guidance.² We obtained data from FDA on inspections, compliance actions, and recalls from 2003 to 2015, as well as adverse events from 2001 to 2015 that were linked to compounding of drugs for animals. To assess the reliability of FDA's data we reviewed agency documentation of the systems used to collect and record the data and interviewed officials knowledgeable about those systems. We determined the data are sufficiently reliable for the purposes of determining FDA's actions to regulate compounding animal drugs. We also interviewed FDA's veterinary, regulatory, and drug evaluation officials in headquarters offices and the FDA district offices responsible for regulatory oversight in four states we selected for in-depth review of their efforts to monitor drug compounding and the extent to which the states collaborate with FDA district offices. We reviewed relevant state statutes and regulations concerning compounding and interviewed representatives of boards of pharmacy and veterinary medicine, veterinary medical associations and pharmacies, and the horse-racing industry. The information we obtained from these states is not generalizable, but it provided us with a greater understanding of key issues involved in drug compounding for animals.

We conducted this performance audit from June 2014 to September 2015 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

²GAO, *Standards of Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: Nov. 1999); Office of Management and Budget, *Final Bulletin for Agency Good Guidance Practices*, OMB Memorandum M-07-07 (Washington, D.C.: 2007).

Appendix II: Scientific Studies Reviewed That Address the Quality of Drugs Compounded for Animals

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Ciribassi, John, Andrew Luescher, Kirby S. Pasloske, Carol Robertson-Plouch, Alan Zimmerman, and Liane Kaloostian-Whittymore. "Comparative Bioavailability of Fluoxetine after Transdermal and Oral Administration to Healthy Cats." *American Journal of Veterinary Research*, vol. 64 (2003): 994-998.

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Krotscheck, Ursula, Dawn Merton Boothe, and Harry Boothe. "Evaluation of Transdermal Morphine and Fentanyl Pluronic Lecithin Organogel Administration in Dogs." *Veterinary Therapeutics*, vol. 5, no. 3 (2004): 202-211.

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Mawby, D.I., J.C. Whittemore, S. Genger, and M.G. Papich. "Bioequivalence of Orally Administered Generic, Compounded, and Innovator-Formulated Itraconazole in Healthy Dogs." *Journal of Veterinary Internal Medicine*, vol. 28 (2014): 72-77.

Mealey, K.L., K.E. Peck, B.S. Bennett, R.K. Sellon, G.R. Swinney, K. Melzer, S.A. Gokhale, and T.M. Krone. "Systemic Absorption of Amitriptyline and Buspirone after Oral and Transdermal Administration to Healthy Cats." *Journal of Veterinary Internal Medicine*, vol. 18 (2004): 43-46.

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Robertson, S.A, P.M. Taylor, J. W. Sear, and G. Keuhnel. "Relationship between Plasma Concentrations and Analgesia after Intravenous Fentanyl and Disposition after Other Routes of Administration in Cats." *Journal of Veterinary Pharmacology and Therapeutics*, vol. 28 (2005): 87-93.

Sartor, Laura Lee, Lauren A. Trepanier, Mandy M. Kroll, Ilona Rodan, and Laura Challoner. "Efficacy and Safety of Transdermal Methimazole in the Treatment of Cats with Hyperthyroidism." *Journal of Veterinary Internal Medicine*, vol. 18 (2004): 651-655.

Scott-Moncrieff, J. Catherine R., George E. Moore, Jasmine Coe, Randy C. Lynn, Wilson Gwin, and Raymond Petzold. "Characteristics of Commercially Manufactured and Compounded Protamine Zinc Insulin." *Journal of the American Veterinary Medical Association*, vol. 240 (2012): 600-605.

Smith, Joseph A., Mark G. Papich, Gregg Russell, and Mark A. Mitchell. "Effects of Compounding on Pharmacokinetics of Itraconazole in Black-Footed Penguins (*Spheniscus demersus*)." *Journal of Zoo and Wildlife Medicine*, vol. 41, no. 3 (2010): 487-495.

Stanley, S.D., S.M. Thomas, and W. Skinner. "Comparison for Pharmaceutical Equivalence of FDA-Approved Products and Compounded Preparations of Ketoprofen, Amikacin, and Boldenone." *American Association of Equine Practitioners*. Ithaca, NY: International Veterinary Information Service (2003).

Thompson, Jessica A., Mustajab H. Mirza, Steven A. Barker, Timothy W. Morgan, Rudy W. Bauer, and Rebecca S. McConnico. "Clenbuterol Toxicosis in Three Quarter Horse Racehorses after Administration of a

Compounded Product.” *Journal of the American Veterinary Medical Association*, vol. 239 (2011): 842-849.

Umstead, Meghan E., Dawn M. Boothe, Crisanta Cruz-Espindola, John M. MacDonald, Robert Kennis, and Donna Angarano. “Accuracy and Precision of Compounded Ciclosporin Capsules and Solution.” *Veterinary Dermatology*, vol. 23 (2012): 431-482.

Willis-Goulet, Heather S., Bill A. Schmidt, Constance F. Nicklin, Rosanna Marsella, Gail A. Kunkle, and Ian R. Tebbett. “Comparison of Serum Dexamethasone Concentrations in Cats after Oral Or Transdermal Administration Using Pluronic Lecithin Organogel (PLO): A Pilot Study.” *Veterinary Dermatology*, vol. 14 (2003): 83-89.

Appendix III: Excerpt from FDA Voluntary Reporting Form for Adverse Drug Events

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration Center for Veterinary Medicine		Form Approved: OMB No. 0910-0645 Expiration Date: 4/30/2016 (See mailer page for Burden Statement)
VETERINARY ADVERSE DRUG REACTION, LACK OF EFFECTIVENESS, OR PRODUCT DEFECT REPORT <i>(For VOLUNTARY Reporting)</i>		
<i>NOTE: This report is authorized by 21 U.S.C 352 (a) and (f). While you are not required to report, your cooperation is needed to assure comprehensive and timely assessment of product labeling.</i>		
Individual Case Safety Report Number (FDA Assigned Number)		Submission Type <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up
Report Type <input type="checkbox"/> Adverse Event <input type="checkbox"/> Product Problem <input type="checkbox"/> Both Adverse Event and Product Problem		
Date of this Report (mm/dd/yyyy) Month <input type="text"/> Day <input type="text"/> Year <input type="text"/>		Date of Initial Report (If this report is a follow-up) (mm/dd/yyyy) Month <input type="text"/> Day <input type="text"/> Year <input type="text"/>
Sender Information		
First Name		Last Name
Street Address		
City	State or Province	Postal/ZIP Code
Country	Telephone Number	Telephone Number (Other)
Fax Number	Email Address	
Sender Category <input type="checkbox"/> Veterinarian <input type="checkbox"/> Animal Owner <input type="checkbox"/> Physician <input type="checkbox"/> Patient <input type="checkbox"/> Other Health Care Professional <input type="checkbox"/> Other <input type="checkbox"/> Unknown		
Sender Previously Reported to the Manufacturer? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, provide the Manufacturer's Case Number: _____		
No Identity Disclosure <input type="checkbox"/> If you do NOT want your identity disclosed to the manufacturer, mark this box.		
Preferred Method of Contact <input type="checkbox"/> Telephone <input type="checkbox"/> Email		
Health Care Professional Information (If different from Sender Information)		
First Name		Last Name
Street Address		
City	State or Province	Postal/ZIP Code
Country	Telephone Number	Telephone Number (Other)
Fax Number	Email Address	
FORM FDA 1932a (10/13)		Page 1

**Appendix III: Excerpt from FDA Voluntary
Reporting Form for Adverse Drug Events**

Owner Information <i>(If different from Sender Information)</i>		
First Name	Last Name	
Street Address		
City	State or Province	Postal/ZIP Code
Country	Telephone Number	Telephone Number (Other)
Fax Number	Email Address	
Suspected Product Information		
Name of Suspected Product		
Diagnosis and/or Reason for Use of the Product		
Dosage Form (Chewable, liquid, tablet, topical, injection, etc.)		
Date of First Exposure <i>(mm/dd/yyyy)</i>	Date of Last Exposure <i>(mm/dd/yyyy)</i>	
Month <input type="text"/> Day <input type="text"/> Year <input type="text"/>	Month <input type="text"/> Day <input type="text"/> Year <input type="text"/>	
Duration of Product Use		
Product Use Information for Suspected Product		
Dose Administered		
Interval of Administration (Frequency)		
Route of Administration		
Product Administered By		
<input type="checkbox"/> Veterinarian/Veterinary Staff <input type="checkbox"/> Owner <input type="checkbox"/> Other		
Lot Number	Expiration Date <i>(mm/dd/yyyy)</i>	
	Month <input type="text"/> Day <input type="text"/> Year <input type="text"/>	
Name of Manufacturer of Suspected Product		
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Appendix III: Excerpt from FDA Voluntary Reporting Form for Adverse Drug Events

Adverse Event Information	
Veterinarian's Level of Suspicion that Product Caused the Adverse Event	
<input type="checkbox"/> High <input type="checkbox"/> Medium <input type="checkbox"/> Low <input type="checkbox"/> Unknown	
Treatment of Adverse Event (<i>Describe briefly</i>)	
Did Adverse Event Abate After Stopping the Product?	
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not Applicable	
Did Adverse Event Reappear After Reintroduction of the Product?	
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not Applicable	
Outcome	
<input type="checkbox"/> Recovered <input type="checkbox"/> Died <input type="checkbox"/> Other	
Species and Related Information	
<input type="checkbox"/> Budgerigar	<input type="checkbox"/> Cat
<input type="checkbox"/> Dog	<input type="checkbox"/> Ferret
<input type="checkbox"/> Horse	<input type="checkbox"/> Human
<input type="checkbox"/> Sheep	<input type="checkbox"/> Other (<i>Specify</i>): _____
<input type="checkbox"/> Cattle	<input type="checkbox"/> Cockatiel
<input type="checkbox"/> Fish	<input type="checkbox"/> Goat
<input type="checkbox"/> Parrot	<input type="checkbox"/> Pig
<input type="checkbox"/> Guinea Pig	<input type="checkbox"/> Rabbit
Breed	Gender
	<input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Male Neutered <input type="checkbox"/> Female Neutered
Age:	Weight:
Overall Health Status When Suspected Product Given	
<input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor <input type="checkbox"/> Critical	Number of Animals Treated: _____
	Number of Animals Affected: _____
Adverse Event Occurrence	
Date of Onset of Adverse Event (<i>mm/dd/yyyy</i>)	
Month <input type="text"/> Day <input type="text"/> Year <input type="text"/>	
<i>Length of Time Between First Exposure to Suspected Product(s) and Onset of Adverse Event</i>	<i>Length of Time Between Last Administration of Suspected Product(s) and Onset of Adverse Event</i>
_____	_____
When the Adverse Event Occurred, Treatment with Suspected Product	
<input type="checkbox"/> Had already been completed <input type="checkbox"/> Was discontinued <input type="checkbox"/> Was discontinued and replaced with another product <input type="checkbox"/> Was discontinued and reintroduced later <input type="checkbox"/> Was continued at an altered dose <input type="checkbox"/> Other (<i>Specify</i>): _____	
Document Information	
Attached Document Name (<i>Filename if Electronic</i>)	

Attached Document Description	

Attached Document Name (<i>Filename if Electronic</i>)	

Attached Document Description	

Attached Document Name (<i>Filename if Electronic</i>)	

Attached Document Description	

FORM FDA 1932a (10/13)	Page 3

Appendix III: Excerpt from FDA Voluntary Reporting Form for Adverse Drug Events

Concurrent Clinical Problem(s)

Were There Concurrent Clinical Problems?

Yes No Do not know None

List Concurrent Clinical Problem(s).

Concurrent Product Information (Excluding Treatment of Current Event)

Please provide name(s), dose(s), interval(s), date(s) of treatment(s), and other relevant information to describe other products that the patient was taking at the time of the event. Either copy this section as needed (you may fill out this section in other copies of this form) or provide comments in the long narrative section that follows this one.

Were Concurrent Products Given?

Yes No Do not know None

List Names of Concurrent Products Administered.

Date of First Exposure (mm/dd/yyyy)

Month Day Year

Date of Last Exposure (mm/dd/yyyy)

Month Day Year

Duration of Product Use

Adverse Event/Product Problem (Long Narrative)

Describe the Adverse Event/Product Problem.

**Appendix III: Excerpt from FDA Voluntary
Reporting Form for Adverse Drug Events**

Adverse Event/Product Problem (Long Narrative, Continued)

If more space is needed, continue description below of the Adverse Event/Product Problem.

Appendix IV: Key Provisions of FDA's Draft Guidance for Industry on Animal Drug Compounding

In May 2015, the Food and Drug Administration (FDA) published a notice in the *Federal Register* stating it had withdrawn Compliance Policy Guide Section 608.400 and in the same notice announced it was seeking comments on its draft Guidance for Industry, No. 230. The draft guidance would apply only to entities compounding animal drugs from bulk active pharmaceutical ingredients (bulk substances)—specifically state-licensed pharmacies and veterinarians, and facilities that register with FDA as outsourcing facilities under the Federal Food, Drug, and Cosmetic Act. The draft guidance, for which FDA was receiving public comments at the time of our review, states that generally, the agency does not intend to take action against a state-licensed pharmacy, a licensed veterinarian, or an FDA-registered outsourcing facility¹ under a certain provision of the Federal Food, Drug, and Cosmetic Act if these entities compound animal drugs from bulk active pharmaceutical ingredients² in accordance with the conditions described below, and the drug is not otherwise adulterated or misbranded.³ The draft guidance states that entities should keep adequate records to demonstrate that the necessary conditions have been met. Table 1 below shows FDA's stated conditions in the draft guidance for each of the three types of compounders.

¹The Federal Food, Drug, and Cosmetic Act permits drug compounders to register with FDA as "outsourcing facilities." An outsourcing facility is defined in the Federal Food, Drug, and Cosmetic Act as a facility at one geographic location or address that (1) is engaged in the compounding of sterile drugs; (2) has elected to register as an outsourcing facility; and (3) complies with all of the requirements stated in the applicable provision of the act. 21 U.S.C. 353b. An outsourcing facility must report to FDA certain information about the drug products it compounds. If certain requirements are met, drugs that the facility compounds can qualify for exemptions from FDA new drug approval and select labeling requirements. Outsourcing facilities registered with FDA will be subject to inspection.

²In this report, to avoid confusion, we use the term bulk active pharmaceutical ingredients to indicate "bulk substances," a term used by FDA. FDA defines a bulk drug substance as any substance that is represented for use in a drug and that when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug.

³A drug is deemed adulterated under the Federal Food, Drug, and Cosmetic Act if it consists in whole or in part of any filthy, putrid, or decomposed substance or has been prepared, packed, or held under unsanitary conditions, among other things. 21 U.S.C. § 351. A drug is deemed misbranded if, among other things, the labeling is false or misleading. 21 U.S.C. § 352.

**Appendix IV: Key Provisions of FDA's Draft
Guidance for Industry on Animal Drug
Compounding**

Table 1: Conditions under Which the FDA Has Proposed Not to Take Enforcement Action against Entities Compounding Animal Drugs from Bulk Active Pharmaceutical Ingredients

Type of condition applied to compounding entities	State-licensed pharmacies	Licensed veterinarians	Food and Drug Administration (FDA)-registered outsourcing facilities
Licensing	The drug is compounded by or under the direct supervision of a licensed pharmacist.	The drug is compounded and dispensed by a licensed veterinarian to treat an individually identified animal patient under his or her care.	The drug is compounded by or under the direct supervision of a licensed pharmacist.
Drug dispensing	The drug is dispensed after the receipt of a valid prescription from a veterinarian for an individually identified animal patient that comes directly from the prescribing veterinarian or from the patient's owner or caretaker to the compounding pharmacy. The drug is not sold or transferred by an entity other than the entity that compounded such drug. ^a	The drug is not sold or transferred by the veterinarian compounding the drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by the veterinarian to a patient under his or her care, or the dispensing of an animal drug compounded by the veterinarian to the owner or caretaker of an animal under his or her care. ^a	The drug is not sold or transferred by an entity other than the outsourcing facility that compounded such drug. ^a
Quantity produced	A drug may be compounded in advance of receipt of a prescription in a quantity that does not exceed the amount of drug product that the state-licensed pharmacy compounded pursuant to patient-specific prescriptions based on a history of receipt of such patient-specific prescriptions for that drug product over any consecutive 14-day period within the previous 6 months.		
Drug administration to food animals	The drug is not intended for use in food-producing animals, and the prescription or documentation accompanying the prescription for the drug contains the statement "This patient is not a food-producing animal." ^b	The drug is not intended for use in food-producing animals.	The drug is not intended for use in food-producing animals, and the prescription or order, or documentation accompanying the prescription or order, for the drug contains the statement, "This drug will not be dispensed for or administered to food-producing animals."

**Appendix IV: Key Provisions of FDA's Draft
Guidance for Industry on Animal Drug
Compounding**

Type of condition applied to compounding entities	State-licensed pharmacies	Licensed veterinarians	Food and Drug Administration (FDA)-registered outsourcing facilities
No alternative FDA-approved drugs are available	<p>If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drug, and</p> <ul style="list-style-type: none"> • there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care; and • the prescription or documentation accompanying the prescription contains a statement that the change between the compounded drug and the FDA-approved drug would produce a clinical difference for the individually identified animal patient.^c 	<p>If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drug, there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care.^c</p> <p>There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) and (5) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b(a)(4), (5)) and part 530 of the <i>U.S. Code of Federal Regulations</i> to appropriately treat the disease, symptom, or condition for which the drug is being prescribed.^d</p>	<p>The drugs are compounded only from bulk drug substances designated by FDA and included as part of the Guidance for Industry, No. 230.^e</p> <p>The veterinarian's prescription or order states that the drug is intended to treat the species and condition(s) for which the substance is listed in the Guidance for Industry, No. 230.^e</p>

**Appendix IV: Key Provisions of FDA's Draft
Guidance for Industry on Animal Drug
Compounding**

Type of condition applied to compounding entities	State-licensed pharmacies	Licensed veterinarians	Food and Drug Administration (FDA)-registered outsourcing facilities
Documentation	<p>If there is an FDA-approved animal or human drug with the same active ingredient(s), the pharmacy determines that the compounded drug cannot be made from the FDA-approved drug(s), and documents that determination.</p> <p>The pharmacy receives from the veterinarian (either directly or through the patient's owner or caretaker), in addition to any other information required by state law, the following information, which can be documented on the prescription or documentation accompanying the prescription:</p> <ul style="list-style-type: none"> • identification of the species of animal for which the drug is prescribed; and, • the statement "There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) and (5) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b(a)(4), (5)) and part 530 of the <i>U.S. Code of Federal Regulations</i> to appropriately treat the disease, symptom, or condition for which this drug is being prescribed." 		<p>All drugs compounded for animals by an outsourcing facility are included on the report required by section 503B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 353b) to be submitted to the FDA each June and December identifying the drugs made by the outsourcing facility during the previous 6-month period.^f</p>
Sources of bulk ingredients	<p>Any bulk drug substance used to compound the drug is manufactured by an establishment that is registered under section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360) (including a foreign establishment that is registered under section 510(i)) and is accompanied by a valid certificate of analysis.^g</p>	<p>Any bulk drug substance used to compound the drug is manufactured by an establishment that is registered under section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360) (including a foreign establishment that is registered under section 510(i)) and is accompanied by a valid certificate of analysis.^g</p>	<p>Any bulk drug substance used to compound the drug is manufactured by an establishment that is registered under section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360) (including a foreign establishment that is registered under section 510(i)) and is accompanied by a valid certificate of analysis.^g</p>

**Appendix IV: Key Provisions of FDA's Draft
Guidance for Industry on Animal Drug
Compounding**

Type of condition applied to compounding entities	State-licensed pharmacies	Licensed veterinarians	Food and Drug Administration (FDA)-registered outsourcing facilities
Adherence to U.S.Pharmacopeia	The drug is compounded in accordance with Chapters 795 and 797 of the United States Pharmacopeia and National Formulary ((USP—NF), (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter 797, Table 1).	The drug is compounded in accordance with USP—NF Chapters 795 and 797 (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter 797, Table 1)).	The drug is compounded in accordance with current Good Manufacturing Requirements. FDA intends to determine whether this condition is met by evaluating whether the facility complies with FDA regulations applicable to current Good Manufacturing Requirements for compounding of human drugs by outsourcing facilities. ^h
Adverse events reporting	Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the pharmacy reports it to FDA on Form FDA 1932a. ⁱ	Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs the veterinarian compounded from bulk drug substances, he or she reports it on Form FDA 1932a. ⁱ	Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the outsourcing facility reports it on Form FDA1932a. ⁱ

**Appendix IV: Key Provisions of FDA's Draft
Guidance for Industry on Animal Drug
Compounding**

Type of condition applied to compounding entities	State-licensed pharmacies	Licensed veterinarians	Food and Drug Administration (FDA)-registered outsourcing facilities
Labeling	The label of any compounded drug indicates the species of the intended animal patient, the name of the animal patient, and the name of the owner or caretaker of the animal patient.	The label of any compounded drug indicates the species of the intended animal patient, the name of the animal patient, and the name of the owner or caretaker of the animal patient.	<p>The label of the drug includes the following:</p> <ul style="list-style-type: none"> • active ingredient(s); • dosage form, strength, and flavoring, if any; • directions for use, as provided by the veterinarian prescribing or ordering the drug; • quantity or volume, whichever is appropriate; • the statement "Not for resale;" • the statement "For use only in [fill in species and any associated condition or limitation listed in Appendix A];" • the statement "Compounded by [name of outsourcing facility];" • lot or batch number of drug; • special storage and handling instructions; • date the drug was compounded; • beyond use date of the drug; • name of veterinarian prescribing or ordering the drug; • the address and phone number of the outsourcing facility that compounded the drug; • inactive ingredients; • the statement "Adverse events associated with this compounded drug should be reported to FDA on a Form FDA 1932a;" and • if the drug is compounded pursuant to a patient specific prescription, the species of the animal patient, name of the animal patient, and name of the owner or caretaker of the animal patient.

Source: GAO analysis of FDA Guidance for Industry (No. 230). | GAO-15-671

**Appendix IV: Key Provisions of FDA's Draft
Guidance for Industry on Animal Drug
Compounding**

^aThe draft guidance states that a sale or transfer of the compounded drug does not include a veterinarian administering the drug to a patient under the veterinarian's care. The sale or transfer of a drug by a pharmacy to a person or another entity is called "dispensing" a drug while the act of giving a medication to an animal is called "administering" a drug.

^bFDA's draft guidance states that all cattle, swine, chicken, turkey, sheep, goats, and nonornamental fish are considered food-producing animals regardless whether the specific animal or food from the specific animal is intended to be introduced into the human or animal food chain. Accordingly, FDA considers pet pot-bellied pigs and pet chicks to be food-producing animals. In addition, the draft guidance specifies that any other animal designated on the prescription or in documentation accompanying the prescription by the veterinarian as a food-producing animal, regardless of species, is considered to be a food-producing animal, such as rabbits, captive elk, and captive deer.

^cFor example, the veterinarian could state that, "Compounded drug X would produce a clinical difference for the individually identified animal patient because the approved drug is too large a dose for the animal and cannot be divided or diluted into the small dose required."

^dExtralabel use means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses. 21 C.F.R. § 530.3(a).

^eThe draft guidance did not identify the bulk active pharmaceutical ingredients (bulk substances) or the animal health conditions these ingredients may treat, but stated that FDA would identify them later with input from the public.

^fInformation that FDA requests registered facilities to provide the agency twice per year includes the active ingredient(s); and the source of the active ingredient(s); the strength of the active ingredient(s) per unit; the dosage form and route of administration; the package description; the number of individual units produced; and the National Drug Code number of the active ingredients, if available, and the final product, if assigned. FDA suggests that registered facilities for sterile drug products (called outsourcing facilities), identify which of the drugs they report biannually to FDA were intended for animal use.

^gAccording to FDA's draft guidance for industry regarding good manufacturing practices, certificates of analysis contain key information about the bulk active pharmaceutical ingredient(s) and testing information to ensure the ingredients are as specified on the label. This information includes the name of the active pharmaceutical ingredient, its grade, the batch number, the date of release, and expiration date. The certificate should list tests performed and the numerical test results obtained, it should be dated and signed by authorized personnel, and include the name, address, and telephone number of the original manufacturer, among other things.

^hFDA enforces regulations called Current Good Manufacturing Practices. According to FDA, these regulations require proper design, monitoring, and control of manufacturing processes and facilities, including the use of strong quality management systems, appropriate quality raw materials, robust operating procedures, and reliable testing laboratories, among other things.

ⁱForm 1932A is the form FDA uses to collect voluntary reports of adverse events associated with animal drugs. See appendix III for a copy of this form.

Appendix V: Examples of Legal Challenges to Food and Drug Administration Authority to Regulate Compounding Drugs for Animals

Year filed	Case name	Key issue considered	Summary of decision
2011	United States vs. Franck's Lab, Inc. ^a	Whether the Food and Drug Administration (FDA) has the authority to prevent a pharmacy from compounding drugs for animals from bulk active pharmaceutical ingredients under the Federal Food, Drug, and Cosmetic Act.	The U.S. District Court, Middle District of Florida, held "that, in enacting the [Federal Food, Drug, and Cosmetic Act] in 1938, Congress did not intend to give the FDA per se authority to enjoin the long-standing, widespread, state-regulated practice of pharmacists filling a veterinarian's prescription for a nonfood-producing animal by compounding from bulk substances." 816 F. Supp. 2d 1256. FDA appealed, but the case was subsequently vacated by the appeals court on appeal by joint motion of the parties, however, because the defendants stopped compounding animal drugs from bulk active pharmaceutical ingredients. 2012 WL 10234948.
2008	Medical Center Pharmacy v. Mukasey ^b	Whether drugs compounded for human and animal use are new drugs and subject to FDA's approval, and whether federal law permits compounding drugs from bulk active pharmaceutical ingredients for nonfood animals.	The U.S. Court of Appeals for the Fifth Circuit ruled that compounded drugs are "new animal drugs" under the Federal Food, Drug, and Cosmetic Act, and are subject to FDA's approval unless the drugs meet the relevant qualifications of the Animal Medicinal Drug Use Clarification Act of 1994. 536 F.3d 408.
2005	Wedgewood Village Pharmacy, Inc. vs. United States ^c	Whether a pharmacy is exempt from FDA's general inspection authority under the Federal Food, Drug, and Cosmetic Act and whether or not a pharmacy suspected of large-scale compounding is covered by the pharmacy exemption for inspection of records under the Federal Food, Drug, and Cosmetic Act.	The U.S. Court of Appeals for the Third Circuit held that pharmacies are not exempt from FDA's general inspection authority, and despite the statutory exemption for pharmacies from records inspection provisions for pharmacies, FDA does not violate due process by conducting records inspections when there is probable cause to believe that the exemption does not apply. 421 F.3d 268-275.
1989	United States vs. Algon Chemical, Inc. ^d	Whether FDA can enforce regulations that essentially limit the sale of new bulk pharmaceuticals to holders of "new animal drug applications." Specifically, whether FDA could prevent a firm from distributing bulk active pharmaceutical ingredients to veterinarians for use in compounding animal drugs if the firm failed to abide by labeling requirements.	The U.S. Court of Appeals for the Third Circuit held that FDA acted within its statutory authority in promulgating and enforcing regulations. 879 F.2d 1155.

Source: GAO analysis of court documents. | GAO-15-671

^a816 F. Supp. 2d 1209 (M.D. Fla. 2012) vacated by 12 WL 10234948 (11th Cir. Oct. 18, 2012).

^b536 F.3d 383 (5th Cir. 2008).

**Appendix V: Examples of Legal Challenges to
Food and Drug Administration Authority to
Regulate Compounding Drugs for Animals**

^c421 F.3d 263 (3rd Cir. 2005).

^d879 F.2d 1154 (3rd Cir. 1989).

Appendix VI: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

SEP 08 2015

Steve Morris
Director, Natural Resources and Environment Team
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Mr. Morris:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "Regulation of Drug Compounding for Use in Animals" (GAO-15-671).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in black ink that reads "Jim R. Esquea".

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

**GENERAL COMMENTS OF THE FOOD AND DRUG ADMINISTRATION (FDA) ON
THE GOVERNMENT ACCOUNTABILITY OFFICE's (GAO) DRAFT REPORT
ENTITLED "DRUG COMPOUNDING FOR ANIMALS: FDA COULD IMPROVE
OVERSIGHT WITH BETTER INFORMATION AND GUIDANCE" (GAO-15-671)**

The Food and Drug Administration (FDA) appreciates the opportunity to review and comment on the draft report. FDA has made substantial progress and has taken an active and deliberative role addressing animal drug compounding, proposing a framework intended to balance competing objectives and reducing the risk of harm to human and animal health. The Agency generally agrees with GAO's recommendations and FDA's work in this program area is ongoing. Fiscal year 2015 accomplishments to date include:

- Withdrawing the outdated 2003 Compliance Policy Guide 608.400 and simultaneously publishing a draft Guidance for Industry #230, Compounding Animal Drugs from Bulk Drug Substances.
- Hiring a Compounding Coordinator who reports directly to the Director of the Office of Surveillance and Compliance to oversee all compounding related to Center for Veterinary Medicine activities.
- Hiring 3 Veterinary Medical Officers, 2 Consumer Safety Officers, and 1 Regulatory Counsel to assist in matters related to animal drug compounding.
- Expanding the Animal and Veterinary Compliance and Enforcement webpage to include a page dedicated to Inspections, Recalls, and Other Actions with Respect to Firms that Engage in Animal Drug Compounding.

GAO Recommendation

Modify the voluntary reporting form FDA uses to obtain information on adverse events to ask whether drugs involved in adverse events were compounded.

FDA Response

FDA agrees with the GAO recommendation to modify the voluntary reporting form for veterinary adverse events (Form FDA 1932a) to seek information about whether the involved drug(s) were compounded. Steps are being taken to revise the Form FDA 1932a to specifically ask whether the product is compounded. However, changing the form will not rectify other factors that may have a larger impact on the adverse event reporting, including the voluntary nature of reporting, the fact that many reporters of adverse events may not know that the drug is compounded because the drugs are not usually labeled as compounded products, and the limited information about the extent of compounding for animals (i.e., denominator data).

GAO Recommendation

Develop policy or guidance for agency staff that specifies circumstances under which FDA will or will not enforce compounding regulations for animals and clearly define key terms.

FDA Response

FDA agrees with this recommendation and notes that it has already published a draft Guidance for Industry #230 (GFI #230) Compounding Animal Drugs from Bulk Drug Substances. FDA did not leave stakeholders without any indication of its current thinking on this issue, as stated by

GAO on page 14 of the report, because at the same time FDA withdrew the outdated 2003 guidance, it published draft GFI #230, Compounding Animal Drugs from Bulk Drug Substances. The comment period for the draft guidance closes on November 16, 2015, and FDA intends to take comments into consideration in quickly finalizing the guidance. Once the guidance is finalized, the document will explain FDA's current thinking with respect to compounding animal drugs from bulk drug substances.

GAO Recommendation

Consistently document the bases for FDA's decisions about how or whether it followed up on warning letters, adverse event reports, and complaints about drug compounding for animals.

FDA Response

FDA generally agrees with this recommendation. One of FDA's key initiatives is to develop and implement an enforcement strategy that addresses unapproved new animal drugs, including compounded animal drugs. As part of this initiative, FDA will document its actions with respect to follow-up on warning letters, adverse event reports and complaints.

Appendix VII: GAO Contact and Staff Acknowledgments

GAO Contact

Steve D. Morris, (202) 512-3841 or morriss@gao.gov

Staff Acknowledgments

In addition to the individual named above, Mary Denigan-Macauley (Assistant Director), Kevin Bray, Karen Howard, Andrew C. Moore, Cynthia Norris, Stuart Ryba, Kiki Theodoropoulos, Ginny Vanderlinde, and Shana Wallace made key contributions to this report.

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