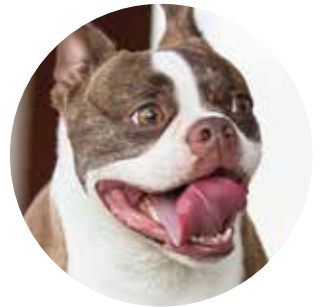


THE ADVANTAGES OF

cGMP

**Manufactured
Veterinary Drugs**



VS

**Compounded
Drugs -**

WHY IT MATTERS



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Veterinary medicine
has been debating
the practice and
regulation of
compounding
for over 20 years.

—Mark Papich, DVM, MS, DACVCP



Consistently manufactured animal drug products made in facilities that adhere to current Good Manufacturing Practices (cGMP) are designed with the veterinarian, client, and pet in mind. Use of stringent, essential processes results in a consistent product that guarantees quality, safety, and convenience and instills confidence in the veterinarian who prescribes them. While compounding drugs for veterinary patients has been a common practice for many years, the US Food and Drug Administration (FDA) is taking a closer look at the animal drug compounding requirements presently in place, largely due to problems that have occurred with use of compounded sterile preparations for human patients, in some cases with devastating outcomes.¹

The US Congress passed “The Drug Quality and Security Act” in November 2013 to ensure better quality of sterile compounded drugs. But the act has several shortcomings, including the fact that it does not regulate veterinary compounding. Some critics feel that the language of the 2013 law actually enables some compounders, particularly individual pharmacies that compound animal drugs, to operate without concerns about federal enforcement.

On the following pages, you’ll find the answers to questions many veterinarians have about the differences between cGMP manufactured and compounded products. This information is intended to help veterinarians make the best possible recommendations—for both their patients and for their practice. The decision to use cGMP manufactured products can be part of an overall plan to manage a veterinary practice’s aggregate liability.

What Are “Manufactured” Drugs?



Manufacturing means the production, preparation, propagation, conversion, or processing of a drug, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis.²

Manufacturing includes the packaging or repackaging of a drug or the labeling or relabeling of the container of a drug for resale by veterinarians or pharmacies.²

Manufacturing also includes the preparation and promotion of commercially available products from bulk compounds for resale by pharmacies, practitioners, or others. In general, manufacturing differs from compounding in that compounding involves a specific veterinarian–client–patient–pharmacist relationship, the preparation of a relatively small quantity of medication, and different conditions of sale (eg, specific prescription orders). Manufactured drugs, on the other hand, are highly regulated to ensure a consistent, high-quality product and must meet cGMP standards enforced by the FDA to ensure proper design, monitoring, and control of manufacturing processes and facilities.

Manufactured drugs offer significant advantages over compounded drugs (see *sidebar*), including a level of confidence. Veterinarians can rely on the reputation of the company when purchasing drugs from a major pharmaceutical cGMP manufacturer and expect tested, controlled products. In addition, the company has protocols in place to handle any questions and/or adverse event reports from the customer.³

cGMP Manufactured Drug Product Assurances

- Consistent quality – manufactured using current Good Manufacturing Practices (cGMPs) as defined by law
- FDA-inspected production facilities
- Ingredients (active and inactive) confirmed by analysis
- Verified sterile if applicable
- Verified pure
- Confirmed stability and date of expiration
- Compliant with federal and state laws
- Protocols in place to handle any questions and/or adverse event reports from the customer
- If drug is FDA approved:
 - Proved efficacious
 - Stated on label/product insert
 - Identifiable by six-digit New Animal Drug Application (NADA) number or ANADA number if approved generic
 - Monitored over time under field conditions
 - Advertising and promotional materials state truthful descriptions – subject to FDA review
 - Postmarketing communications occur between FDA and veterinarians – adverse events, efficacy issues, and manufacturing defects are reported



What Is Compounding?



According to the FDA, drug compounding is the practice of combining, mixing, or altering the ingredients of a drug by a licensed pharmacist, licensed physician, or a person supervised by a licensed pharmacist to create a medication that meets the needs of a specific

patient.⁴ Examples are mixing two injectable drugs, preparing a suspension from crushed tablets, or adding flavoring to a drug.⁵ The United States Pharmacopeia (USP) further details the definition to include assembling, packaging, and labeling of a drug or device in accordance with a practitioner's prescription or based on a practitioner–patient–pharmacist–compounder relationship established in the course of professional practice.⁶

When Is Compounding Appropriate?

Ease of administration and dispensing are primary factors in formulating animal drugs, resulting in pastes, syringes, flavored tablets, and transdermal medications to make dosing easier on the pet and the owner. But, despite the many new animal drugs available, not all treatment needs have been met. Compounding is necessary when there is no commercially available form of a drug, when a product has been discontinued, or when there is a shortage in availability.⁷

Advantages of cGMP Manufactured Products over Compounded Products

Companies that adhere to cGMPs provide veterinarians with consistently manufactured products to guarantee quality, safety, and convenience for both the client and the veterinarian.

- Within cGMP facilities, the manufacturing standards and ingredients for products are strict enough for human consumption, and products made specifically for animals also must adhere to these standards.
- When products are labeled as cGMP compliant, practitioners can be assured that they are receiving and providing consistent, reliable medications.
- PRN Pharmacal's manufacturing arm, known as Pegasus Laboratories, utilizes the stringent framework of FDA standards to incorporate quality measures that meet or exceed government regulations for EVERY product produced – ***not out of requirement, but out of commitment to quality.***



What Are the Potential Drawbacks of Compounded Drugs?



In general, compounding can profoundly benefit animal patients. Providing drugs for animals in an absorbable, palatable, acceptable form is a true service. Regrettably, these positives can be offset by the drawbacks of compounded drugs: questionable purity, strength, and concentration (Table 1). But the veterinarian who is aware of the potential issues can use the compounding treatment option appropriately.³

Although the FDA recognizes that compounding is important in veterinary practice, the agency must also ensure that compounded drugs do not lack potency, harm animals being treated, or produce residues in food

animals. These are risks that all types of compounding pharmacies aim to minimize.

According to the FDA's Draft Guidance for Industry issued in May 2015,⁸ three different types of compounding activities are identified to provide veterinarians a better understanding of the differences among each activity and how each is held accountable by way of regulation: state-licensed pharmacies, licensed veterinarians, and outsourcing facilities.

A majority of compounding pharmacies operate legally and ethically according to stated requirements. The FDA finds, however, that inspection of some compounders exposes violations, including illegal use of bulk substances; use of bulk substances that have been removed from the human market for safety reasons; unnecessary compounding because there is a manufactured drug that, as labeled, will treat the patient's condition; compounding outside of a valid veterinarian–client–patient relationship; and compounded products inadequately labeled with directions for use as specified by the veterinarian.⁹

Table 1. Comparison of cGMP Manufactured vs Compounded Drug Products

Feature	Advantage	Manufactured Drug	Compounded Drug
FDA inspection of manufacturing facilities	Confirms manufacturer compliance with FDA regulations regarding product quality	Yes	Variable
Manufactured using current Good Manufacturing Practices (cGMPs)	Specifications ensure therapeutic consistency of every batch produced	Yes	No*
Analytic drug testing for quality, strength, purity before release	Confirms product contains what label indicates	Yes	Not Known
Labeled expiration date	Last day that product should be used, based on formulation	Yes	Yes, but product beyond-use-date determined by pharmacist per USP guidelines not by testing
Regular drug stability testing	Ensures expiration date on label matches actual shelf-life	Yes	No

*FDA Draft Guidance does apply to bulk compounding.

Adapted from the Animal Health Institute (AHI), American Veterinary Medical Association (AVMA), and the American Veterinary Distributors Association (AVDA). *Veterinary compounding* [brochure; 2011]. <<http://www.ahi.org/issues-advocacy/animal-drug-compounding/>>.

A comprehensive review of the FDA's draft guidance for industry document on compounding animal drugs from bulk drug substances⁸ is underway. The draft outlines specific conditions for animal drug compounding by state-licensed pharmacies, licensed veterinarians, or outsourcing facilities. Until a final ruling is issued and adhered to, gaps are likely to remain regarding oversight, inspections, and overall compliance, which puts more responsibility on the veterinarian to ensure overall safety of the compounded product.

Are Compounded Drugs the Same as Generics?



Compounded drugs and generic drugs are *not* equivalent!

Generics are FDA approved after an Abbreviated New Animal Drug Application (ANADA) review that ensures they contain the same active ingredient(s), shown to be bioequivalent to the pioneer drug (equivalent safety and efficacy)

and have the same therapeutic effects

as the original, approved, manufactured product.⁹ The FDA does not approve compounded drugs, which eliminates the federal approval process for verifying safe, effective products that meet specific standards and have been checked for manufacturing quality before reaching the public.⁶

FDA-approved pioneer drugs are given a six-digit NADA number; generic drugs receive a unique six-digit ANADA number. Both brand name and generic drug labels or package inserts usually state "Approved by FDA."¹⁰ A compounded product should be labeled that it is not FDA approved.⁹

It is essential for veterinarians to understand the difference between an FDA-approved generic drug and a compounded unapproved drug, and to educate their clients accordingly. Pet owners who are unaware of these differences may order compounded medications outside of their veterinarian's knowledge, possibly putting their pet at risk.

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The words above are quoted from posted warning letters from the FDA to drug compounders regarding violations during the past 10 years. The letters can be found at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm#recent>.

Why Can Compounded Drugs Pose a Risk?

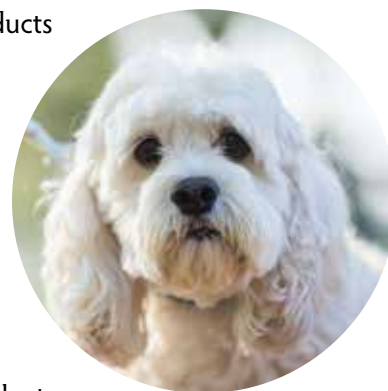
Although traditional pharmacy compounding helps individuals with needs that are not met by commercially available drugs, it is important to recognize that drugs not subject to stated federal cGMP quality standards may be made using poor quality practices. Practitioners should keep in mind that a compounded product can be weaker, stronger, not as pure, or absorbed less effectively than a brand name or generic drug.³ Patients are clearly put at risk if given an ineffective compounded drug rather than a safe, effective, manufactured drug.⁴ Tragically, compounded drugs have even been implicated in the deaths of veterinary patients, most recently horses in Kentucky and Florida (see sidebar on page 7).

Drugs intended for a particular species (including humans) are frequently compounded for another animal species. In such cases, drug absorption may not only be affected by compounding practices but also by the physiological species differences. Although we may assume that absorption is similar among species, the natural variations can result in poor efficacy. Extrapolating to veterinary species from studies that have been performed in people given oral drugs is very difficult. Usually specific studies in animals are required unless the drug involved is extremely stable, soluble, and well absorbed.⁶

Reputable compounding pharmacies produce high-quality medications with promised potency, stability, and beyond-use-dates (BUDs). The USP specifies BUDs for various formulations, but compounding pharmacies

sometimes supply products that go beyond their end date without supporting studies.

The BUD is not the same as an expiration date, which is based on rigorous testing and drug performance. A drug compounded from an approved product is given the same expiration date as the original drug. The compounding pharmacist sets the BUD according to USP parameters and not more than 25% of the approved drug's shelf-life, up to 6 months.⁹



Some drugs are not suitable for compounding because they undergo rapid inactivation or loss of potency. A few compounded antibiotics are actually *subtherapeutic* and can lead to bacterial drug resistance—a risk to both pet and owner. Conversely, compounded products may contain ingredient levels well above the labeled amount, which can be toxic for the pet as well as the owner handling the medication.⁶ All things considered, practitioners should assume that they are responsible for the use and treatment outcome of any compounded product.³

Risks to patients can also occur when drug stability and efficacy are compromised through compounding. Specific examples have been published,⁶ such as use of faulty protective coatings and altered vehicles, exposure to elevated temperature, and improper pH. A pH higher than optimum can result in a significant loss of the active ingredient, and may even render the compounded drug inactive due to oxidation, which can occur if the components are exposed to light and oxygen.

Compounding pharmacies have the responsibility to provide assurances that their formulations meet specific standards and are stable and potent until their BUDs. Voluntary accreditation is available from the Pharmacy Compounding Accreditation Board (PCAB) and signifies a commitment to quality. Accredited pharmacies have high standards and significant checks in place to assure products meet those standards.

Veterinarians need to be aware that compounding may impact the pharmacokinetics of a drug. This may result in drug concentrations that are above or below the therapeutic range and lead to the development of an adverse event, including therapeutic failure.

—AVMA Veterinary
Compounding Policy

Compounding Errors Can Have Tragic Consequences

Lawsuits involving veterinary compounded drugs have made headlines in recent years. These cases illustrate some of the potential risks of compounded drugs and tragic consequences when compounding errors are made.

Compounded drug may have killed four horses, FDA reports

10 horses in Kentucky and Florida affected by EPM treatment
(from <http://veterinarynews.dvm360.com/compounded-drug-may-have-killed-four-horses-fda-reports>)

Pharmacy Behind Fatal Dose That Killed 21 Polo Ponies

(from www.palmbeachpost.com/news/news/owners-of-21-dead-polo-ponies-sue-pharmacy-that-ml/ml564)

Two More Horses Dead After Receiving Compounded Medication

(from www.thehorse.com/articles/33889/two-more-horses-dead-after-receiving-compounded-medication)

Two horses in Kentucky died in March 2014 after application of a compounded drug oral paste containing toltrazuril and pyrimethamine used to treat or prevent equine protozoal myeloencephalitis (EPM). [Note: Approved manufactured EPM treatments are available, including ReBalance® (sulfadiazine/pyrimethamine oral suspension) from PRN Pharmacal.] Necropsy on one of the horses revealed the cause of death to be pyrimethamine poisoning. The owners have filed a civil suit against the compounding pharmacy, Wickliffe Pharmacy, in Lexington, Kentucky. According to court documents, the usual amount of the two drugs found in most pastes to treat EPM is 416 mg/mL of toltrazuril and 17 mg/mL of pyrimethamine. The FDA tested the lot of compounded paste and found it to contain 184 mg/mL of toltrazuril and 283 mg/mL of pyrimethamine. The label of the paste given to one of the Kentucky horses said that the tube contained 227 mg/mL of toltrazuril and 340 mg/mL of pyrimethamine, the latter of which the plaintiffs claim would certainly be enough to kill a horse. In addition, toltrazuril is not approved for use in the horse in the US.¹³

Owners of three Thoroughbreds in Florida have also sued Wickliffe, alleging that Wickliffe prepared a batch of drug designed to treat EPM which contained 13 times the amount of pyrimethamine found in the manufactured formula. The same batch was implicated in the deaths of the two horses in Kentucky. The owners claim that their horses were hospitalized after receiving doses from the same batch, in this case as an oral suspension, and that Wickliffe allegedly shipped the medication to them at an Ocala training center a month after it knew (or should have known) that there was a problem with the batch. The three horses, all of whom were hospitalized, survived but may not be able to return to racing. In all, eight horses at the Ocala center were given the drug. Two died, and six others had neurological disturbances within 36 hours of administration of the compound.¹⁴

In another case, 21 polo ponies died in Florida in April 2009 after being injected with a compounded version of the French-made vitamin supplement Biodyl (Merial), which is banned for sale in the United States. (Compounding pharmacies are prohibited from replicating drugs that are banned in the United States.) Days after the horses collapsed, officials of Franck's Pharmacy admitted they had put too much selenium in the supplement it prepared for the horses. Considered an essential nutrient, selenium is also fatal in large doses. A lawsuit filed by the horses' owners was recently settled, seven years after the incident. During the trial, evidence showed that the lab added 100 times the correct dose, 10% instead of 0.1%, of selenium into the mixture that was to help the ponies recover between matches. The horses began collapsing on the polo fields, all dying within a day.¹⁵



Conclusion



Choosing animal drug products manufactured by companies that adhere to current Good Manufacturing Practices provides veterinarians with a guarantee of quality, safety, and convenience.

When products are labeled as cGMP compliant, practitioners can be assured that they are receiving and providing consistent, reliable medications. While there is a place for compounded drugs in veterinary medicine in specific situations, a cGMP manufactured drug—when available—is always the better choice, which can be part of overall business risk management.

Veterinarians are probably wise, however, to be cautious about claims of stability, quality, and systemic absorption unless the compounding pharmacy can document studies conducted and/or its adherence to accepted pharmaceutical standards.

—Mark Papich, DVM, MS, DACVCP

References

1. US FDA. The special risks of pharmacy compounding (2014, October 14). Web. <<http://www.fda.gov/forconsumers/consumerupdates/ucm107836.htm>>
2. Good compounding practices applicable to state-licensed pharmacies. In: Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy. Park Ridge, Ill: National Association of Boards of Pharmacy; 1993:C.1–C.5.
3. Marcella K. Compounding the issue. DVM360. The CVC Group, 1 May 2001. Web. <<http://veterinarynews.dvm360.com/compounding-issue?rel=canonical>>
4. US FDA. Compounding and the FDA: questions and answers (2015, October 6). Web. <<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm>>
5. Animal Health Institute (AHI). Issues and advocacy: animal drug compounding (n.d.) Web. <<http://www.ahi.org/issues-advocacy/animal-drug-compounding/>>
6. Papich MG. Drug compounding [meeting notes]. Presented at the 2014 ACVIM Forum, Nashville, Tennessee, June 4-7, 2014.
7. American Veterinary Distributors Association. Veterinary compounding (n.d.). Web. <<http://avda.net/newsletter/0704/compounding.pdf>>
8. US FDA. Guidance for Industry #230. Compounding Animal Drugs from Bulk Substances. Web. <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM446862.pdf>.
9. AVMA. Veterinary compounding (n.d.). Web. <<http://www.avma.org/KB/Policies/Pages/Compounding.aspx>>
10. Animal Health Institute (AHI), American Veterinary Medical Association (AVMA), and the American Veterinary Distributors Association (AVDA). Veterinary compounding [brochure; 2011]. <<http://www.ahi.org/issues-advocacy/animal-drug-compounding/>>
11. Galle JB. To seize or not to seize: Top 10 things you should know about seizures. Available from Dr. Galle at info@dogwoodvet.net.
12. AVMA Policy Paper on Veterinary Compounding. Web. www.avma.org/KB/Policies/Pages/Compounding.aspx
13. Voss N. Owners sue Wycliffe Pharmacy, Boarding Farm in connection with horse death. Paulick Report, October 26, 2015. Web. <<http://www.paulickreport.com/news/ray-s-paddock/owners-sue-wickliffe-pharmacy-boarding-farm-veterinarian-in-connection-with-horse-death/>>
14. Angst F. Horse Owners file lawsuits against Wickliffe. Blood Horse, June 11, 2104. Web. <<http://www.bloodhorse.com/horse-racing/articles/113691/horse-owners-file-lawsuits-against-wickliffe>>
15. Musgrave J. Jury awards \$2.5 million in damages in 2009 polo horse deaths. Palm Beach Post, March 18, 2006. Web. <http://www.mypalmbeachpost.com/news/news/local/jury-awards-25-million-in-damages-in-2009-polo-hor/nqn6j/>





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