

Compounding Basics for the Veterinarian

by Dr. Kenton Morgan

Compounded preparations have recently received increased attention in the aftermath of the polo pony fatalities in Florida. Although a tragic event and one that possibly brought less than favorable public attention to our profession, it has provided the incentive for many veterinarians to educate themselves on the issue of compounded medications. As equine veterinarians we recognize there are many safe and effective FDA-approved products available for our use. However, we also acknowledge there are times when the current, approved products in their available dosage forms do not meet the therapeutic needs of a particular patient. It is in this situation when a practitioner may need to consider the use of a compounded preparation.

What is compounding?

Compounding is the manipulation of a drug to create a different drug in order to meet the special needs of a patient. It is key that veterinarians understand compounded preparations are to be used for an equine patient when there is nothing currently available in the appropriate dosage form to treat the special needs of that horse. (The intent of compounding is to provide a customized formulation for a specific need of a specific animal, within the context of a Veterinarian Client Patient Relationship—VCPR.) The rationale being that treatment with a compounded product is better than no treatment at all.

It is important that practitioners understand compounded products do not undergo any type of consistent regulatory oversight. The guidelines for safety, efficacy, potency, stability or purity testing of compounded preparations (see product comparison chart on final page) are largely described in the United States Pharmacopeia (USP). However, enforcement of these guidelines is left up to individual state pharmacy boards and can vary from state to state. Many compounding pharmacies have internal standards and requirements for their preparations; however, requirements are not uniform across the industry.

Deciding to use a compounded preparation

The Animal Medicinal Drug Use Clarification Act (AMDUCA) lays the basic ground rules for compounded preparations. These regulations are summarized here. (It should be noted that AMDUCA deals with the use of “therapeutic” drugs. Products that do not have a defined or recognized therapeutic value fall outside of AMDUCA and therefore the compounding of such drugs would not be permissible.)

- A VCPR must exist.
- There is no FDA-approved, commercially available veterinary or human drug that when used as labeled or in an extra-label manner in its available dosage form and concentration, will appropriately treat the patient.
- The health of the animal must be threatened, or suffering or death may result from failure to use the compounded preparation.
- The compounded product must be compounded by a licensed veterinarian or a licensed pharmacist within the scope of a professional practice.

- The compounded preparation must be made from an FDA-approved commercially available product.
- The product must be safe and effective.
- Veterinarians must comply with extra-label drug use, labeling and record keeping requirements.
- The amount of product compounded must be consistent with the needs of the animal identified in the VCPR-based prescription.
- All relevant state laws relating to compounding must be followed
Guidance on the subject of compounding may be found in guidance documents issued by FDA—Compliance Policy Guidelines, CPG 608.400.

The current requirements justifying use of compounded preparations are restrictive. This is to help ensure these types of products are used only when absolutely necessary. In rare cases, an equine veterinarian may face a disease condition in a horse where there are no FDA-approved veterinary or human products which are available to relieve suffering or prevent the death of the patient. In this case, the veterinarian may need to prescribe a compounded preparation from non FDA-approved ingredients. (A good example is pergolide; there is currently no approved commercial source of pergolide. Because this product is necessary to relieve pain and suffering in horses, the AAEP discussed the situation and the need for this product, with the regulatory authorities. FDA exercises “discretionary enforcement” in allowing this product to be compounded from bulk drug ingredients.) When that occurs:

- The veterinarian is responsible for the safety and efficacy of the compounded preparation.
- The veterinarian and pharmacist should carefully assess whether the use of this substance in a compounded form is consistent with state law and FDA policy.
- The veterinarian and pharmacist should ensure the potency, storage, safe handling and quality of the compounded preparation for use throughout the treatment period.

Choosing a compounding pharmacy

When a practitioner determines it is appropriate to use a compounded preparation, how does he or she choose a reputable compounding service? Much like shopping for other important professional services and products, references from respected colleagues should be considered. You can also check with your state pharmacy board to see if any complaints have been lodged against a particular pharmacy. The FDA has a Web site where any warning letters to a particular pharmacy or manufacturer are posted (www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm) and can be reviewed.

Next, contact the prospective pharmacy and be prepared to ask questions about their business practices as well as the services and products they provide.

Here are some questions to consider when talking with your prospective (or current) compounding pharmacist.

- Is your pharmacy accredited by PCAB (Pharmacy Compounding Accreditation Board)? PCAB is an independent organization which sets industry leading

standards for compounding practices. Membership is voluntary and there is significant investment in time and resources by the pharmacy for this accreditation. The PCAB has been recognized by other veterinary organizations and beginning in 2010, all compounding pharmacies exhibiting at the annual AAEP convention will be required to be PCAB accredited.

- Is your pharmacy licensed with my state board of pharmacy to fill prescriptions?
- What FDA-approved drug will be used to compound the preparation I need?
- How does your pharmacy determine that an ingredient or product is appropriate to be used for compounding?
- How long will it take for you to produce the preparation I need? Compounded preparations produced in large quantities that sit on the shelves for extended periods of time (weeks to months), either at the compounding pharmacy or in your clinic, can have negative effects on stability and potency of the preparation.
- How do you determine potency of your preparations? Will you provide those reports to me?
- How does your pharmacy determine beyond-use dating for your compounded preparations? Beyond-use dating is assigned based on evidence to describe the time period a compounded preparation would retain greater than 90% of its original potency. This information is not commonly generated by most pharmacies. Because stability and potency are unknown for many of these preparations, it is important they be formulated on demand and used as soon as possible.
- Who does the actual compounding, a pharmacist or a technician? Is the technician licensed and certified to compound?
- What is the process in place for compounded preparation recalls?
- How are adverse events reported? (Veterinarians and pharmacists should report all adverse events to the FDA/CVM via FDA form 1932A available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/AnimalDrugForms/UCM048810.pdf> . A veterinarian should also report the event to the state pharmacy board--links to all state boards of pharmacy can be located at www.nabp.net.)
- Does your pharmacy have a quality assurance program? If yes, have them describe it.
- Does your pharmacy report product related problems back to your veterinary customers?
- Requesting a product that is a mimic or “knock-off” of an FDA-approved product—and the pharmacy is willing to supply it, should be a red flag to you and you should seek services from another pharmacy. A couple of examples:
 - a. Will you prepare a flavored phenylbutazone product for me? If yes, choose another pharmacy, there are FDA approved flavored bute products on the market.
 - b. Will you prepare an injectable flunixin meglumine product for me? If yes, choose another pharmacy, there are a number of FDA-approved flunixin injectable products on the market.

Also beware of pharmacies willing to produce a preparation similar to an FDA-approved product but with a minor difference, such as changing a solution from a 10 mg/ml to an 8

mg/ml concentration. This does not constitute legitimate compounding and is an indication the pharmacy is willing to circumvent compounding guidelines and regulations.

Liability issues

Practitioners are focused on providing care that is in the best interest of their patients. Our first priority should be the health and welfare of the horse, an additional priority should be the safety of the caregiver when administering compounded preparations. In the course of providing this service to our patients (and their caregivers) we are also cognizant of potential liability issues. The AVMA/PLIT does not provide explicit guidelines regarding the use of compounded preparations but it does recommend practitioners abide by the AVMA and AAEP guidelines on compounding to lessen their potential liability risk. These guidelines can be easily accessed at the respective Web sites. (Both the AVMA and AAEP guidelines on compounding are consistent with the information in this article.)

It goes without saying, the prescribing veterinarian assumes responsibility/liability when using compounded preparations. Other considerations with regard to liability; the veterinary is responsible for “due diligence” on the compounding pharmacy (as noted above, be sure you are utilizing a reputable pharmacy). Be sure the proper medical and dispensing records are kept and the preparation is properly labeled. From an ethical perspective, it would be prudent for the practitioner to inform the client a compounded preparation is being used to treat his or her animal. The practitioner should also make clients aware of the potential risks associated with using these preparations (this should be done with any product, whether using FDA-approved products or compounded preparations).

Frequently asked questions

What is a “pioneer” drug?

A pioneer drug would be the first drug of its kind or in its “class” to be approved by FDA. The product would have gone through the complete NADA (New Animal Drug Application) process. This process would require extensive data regarding safety, efficacy, manufacturing and quality control. This product would typically be patented and have market exclusivity for a specified period of time.

Are compounded preparations equivalent to generic drug products?

No, compounded preparations are not a generic “anything.” Generic drugs go through an abbreviated new animal drug application (ANADA) process by the FDA/CVM. It must be demonstrated the generic is identical to or bioequivalent to the pioneer product. Generic drug approvals can only be considered after the pioneer drug product’s patent has expired. Generics are manufactured under the same regulatory requirements (GMP—good manufacturing practices) as the pioneer drug in an FDA inspected facility. Compounded preparations are not required to undergo any of these measures.

If compounding from an FDA-approved drug is legal, then what is all the discussion about bulk drugs? We understand that compounding should be performed using FDA-

approved medications. AMDUCA states: “Nothing in this part (section of the act on compounding) shall be construed as permitting compounding from bulk drugs.” However, from a practical perspective we recognize there are at least two circumstances where compounding from bulk drugs may be necessary: 1) the approved drug is not commercially available and 2) the needed compounded preparation cannot be made from the approved drug. As mentioned earlier, pergolide is prepared from a bulk drug source because there is no approved product available and FDA has recognized the need for this preparation.

It is also important to understand that not all bulk drug sources are created equal. Bulk drugs should come from an FDA-registered supplier with an appropriate certificate of analysis. Primary concerns are the purity and potency of these products and the potential for “other” (i.e. melamine and ethylene glycol) ingredients which may pose safety risks. It should be the rare exception where a bulk drug is used for compounded preparations, and not a routine or common practice.

Who can legally compound veterinary preparations?

- A licensed veterinarian within the context of a VCPR.
- A licensed pharmacist on the order (prescription) of a licensed veterinarian within the context of a VCPR.

Where can I find regulatory guidance with respect to veterinary compounding?

Regulations governing drug products (including compounded preparations) include:

- FFDCa (Federal Food Drug and Cosmetic Act)
- AMDUCA
This is the federal statute which addresses veterinary compounding from a broad perspective.
www.fda.gov/cvm/index/amducatoc.htm.
- CPG 608.400 (Compliance Policy Guidelines)
These are not statutes, such as AMDUCA, but they are written by the FDA because the government recognizes there is a legitimate need for compounded products. This document provides direction to FDA field personnel, veterinarians, pharmacists and other interested parties with respect to veterinary compounding. The guidelines help outline where FDA may exercise their “discretionary enforcement” when it comes to compounding practices and products.
www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg608-400.html
- State Pharmacy Board
Every state has a pharmacy board or similar regulatory authority. Any practitioner who uses their own compounded preparations or prescribes compounded preparations in their practice, should familiarize themselves with the applicable state pharmacy requirements.
- United States Pharmacopeia Chapters <795> (non-sterile compounding) and <797> (sterile compounding).
www.usp.org or in the Pharmacists’ Pharmacopeia, 2nd ed, USP.

How can I tell if a pharmacy is licensed to ship compounded products into my state?

Most state boards of pharmacy have online search engines listing licensed pharmacies within the state. Consult www.nabp.net to locate state boards of pharmacy. If you are unable to find a pharmacy listed in your state, call the state board of pharmacy to determine that pharmacy's licensure in your state.

Is cost a justification for using compounded products?

Neither cost nor convenience is a justification for using compounded preparations. Remember, the intent of compounding is to provide a customized formulation for the special needs of a particular patient, when nothing else is available.

How do I know if there is an FDA-approved product available for my use?

The FDA has what is called the "Green Book" which lists the current FDA-approved products and is available on line.

www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/default.htm

The Compendium of Veterinary Products is also a good resource and is also available on line (Via AVMA.org for AVMA members).

These resources may not provide information on current product availability (backorders, etc) you will need to contact the manufacturer directly for that information.

How do I know if the compounded preparation is potent and stable?

The compounding pharmacist should be able to provide a reference for the formula used to prepare the compound as well as stability data testing to support the assigned beyond-use dating. Pharmacists should utilize evidence-based formulas for preparations to be used in veterinary species. While some formula sources are proprietary, the pharmacist is still obligated to provide the veterinarian with evidence supporting the stability and potency of the compound. If an evidence-based formula is not available, USP federal guidelines restrict the beyond-use dating to 14 days for a water-containing preparation, and 180 days for those preparations that do not contain water.

Summary

The veterinarian is obligated to use approved products (per label or in an extr-label manner) when these products are available in the appropriate dosage form for the needs of their patients. When these products do not meet the special needs of an individual patient, there are instances where compounded preparations may be necessary. The veterinarian should understand when it is appropriate to use these preparations and the associated risks with their use. When it is time for a compounded preparation, use a reputable pharmacy and play by the rules. The health and welfare of the horse should be our compass needle when making decisions regarding compounded medications.

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References/Resources

- AAEP, Equine Veterinary Compounding Guidelines www.aaep.org
- AVMA, Compounding Guidelines, COBTA (Council on Biologics and Therapeutic Agents) www.avma.org
- AVMA Veterinary Compounding Education Brochure
http://www.avma.org/issues/drugs/compounding/veterinary_compounding_brochure.asp
- AVMA/PLIT Personal Communication
- Compendium of Veterinary Products (available online to AVMA members):
<http://www.avma.org/onlnews/javma/may03/0305011.asp>
- Crowder TJ, Compounding in Equine Practice—A Pharmacists Perspective, OR VMA Meeting Presentation, Mar 2009
- Davis JL, Effects of Compounding and Storage Conditions on Stability of Pergolide Mesylate, JAVMA, Vol 234, No 3, Feb1, 2009
- Lacroix CA, Illegal Drug Compounding: Your Legal Nightmare Waiting to Happen, AAEP 2003
- Morehead JP, Drug Compounding 101, EVE Feb 2007
- Morehead JP, Drug Compounding 102, EVE Mar 2007
- National Association of Boards of Pharmacy www.nabp.net (Links to state pharmacy boards)
- Pharmacy Compounding Accreditation Board www.pcab.org
- Villalobos A, Compounding Concerns for Animals Near and Dear, Veterinary Practice News, Mar 30, 2009
- www.fda.gov/cvm/index/amducatoc.htm (AMDUCA)
- www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg608-400.html (CPG)
- www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm (Warning Letters)
- www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/AnimalDrugForms/UCM048810.pdf (Adverse Event reporting form)
- www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/default.htm (Green Book)
- www.usp.org (United State Pharmacopeia)

Dr. Morgan is the chair of the AAEP Biological and Therapeutic Agents Committee.

Product Comparison Chart

Requirements	New Animal Drug (Pioneer product)	Generic Animal Drug	Compounded Drug
FDA Approval Required	YES	YES	NO
Drugs tested to prove Safety and Efficacy	YES	YES	NO
Drugs manufactured under current Good Manufacturing Practices (cGMP's)	YES	YES	NO
Manufacturing facilities inspected and approved by FDA	YES	YES	NO
Conduct on-going stability testing of drugs	YES	YES	NO
Labels approved by FDA	YES	YES	NO
Advertising/Promotional material reviewed by FDA	YES	YES	NO
Adverse Events/Lack of Efficacy reported to FDA	YES	YES	NO
Drug Manufacturer Facilities inspected by FDA	YES	YES	NO
Analytical Testing of Product Prior to Release for:			
Strength	YES	YES	NO
Identity	YES	YES	NO
Purity	YES	YES	NO
Potency	YES	YES	NO
Sterility (if applicable)	YES	YES	Possibly