Dealing with Drugs:
Things We Should Be Thinking About, and an Intro to the NWRA Wildlife Formulary

Premise
All of us treating wildlife provide medications to our patients, but we don't always think about some of the other implications involved with handling and administering these compounds.

Legalities
OTC vs. prescription
Controlled drugs = drugs and chemicals with potential for abuse.
5 'schedules' based on potential for abuse and their current use in practice.
- Schedule I drugs - the highest potential for abuse and no accepted use in treatment in the US; e.g., heroin and LSD
- Schedule V drugs - lowest potential for abuse; e.g., cough syrups

Most controlled drugs in wildlife rehabilitation fall into categories III, IV and V. A log must be kept of the receipt and date of these substances, as well as a record of their use (date, amount used, for what purpose, by whom), for 2 years.

Responsible Drug Use (*in the animals*)
Things we can do to avoid or minimize the misuse of drugs in wildlife
- AMDUCA (Animal Medicinal Drug Use Clarification Act of 1994); 'off-label' use of drugs; have agreement with veterinarian
- Use correct drugs in the appropriate quantities, duration, and frequency
- Use sterile technique with injectable drugs
- Randomize injection sites and dilute with fluids to minimize irritation
- Warm drugs to room temperature before giving to animal
- Reconstitute solutions properly
- Date the label on all drugs when opened and/or reconstituted
- Shake drugs in solution before use
- Use the correct route of administration

Drug Withdrawal Times *(Potential harm to predators/hunters)*
Restrictions on drugs used in animals intended for human consumption.
- Prohibited use (http://www.farad.org/eldu/prohibit.asp): diethylstilbestrol (DES), chloramphenicol, nitroimidazoles (including metronidazole), clenbuterol, fluoroquinolones (including Baytril®), glycopeptides, nitrofurans (including nitrofurazone, furazolidone, topical use prohibited as well), gentian violet, and adamantine and neuraminidase inhibitors (anti-influenza drugs)
- Appropriate withdrawal times for medications used in deer http://www.omafra.gov.on.ca/english/livestock/alternat/facts/info_withdrawal.htm
- Appropriate withdrawal times for other species
  - Poultry: http://www.farad.org/vetgram/wdtable.asp
  - Cattle: http://www.pubs.ext.vt.edu/404/404-403/404-403.html (scroll down)

Potential Harmful Effects *(of drugs on rehabilitators)*
<u>*Direct*</u> effects of the drugs on rehabilitators/volunteers.
- Abuse (e.g., controlled substances)
- Allergies (e.g., penicillins)
- Toxins (e.g., chloramphenicol)
- Unpleasant (e.g., DMSO)

Take proper precautions when handling all drugs!

- Careful with needles
- Wear gloves as necessary
- Wash hands afterwards

Potential Harmful Effects *(of drugs on wildlife)*

- Some species may be sensitive to specific drugs
  e.g., Fenbendazole in Columbiformes; ivermectin in turtles
- Some drugs should not be used—or used with care—with renal damage or dehydration
  e.g., Aminoglycocides, sulfonamides

Interactions with other drugs

Details provided in other pharmacology lectures

Check package inserts, PDR, on-line resources and/or your veterinarian

e.g., Clavamox© should not be given to an animal already receiving: betablockers, chloramphenicol, erythromycin, or tetracyclines.

Side Effects

Allergic reactions; Check package inserts, PDR, on-line resources and/or with your veterinarian

Special Cautions

These should be listed on the label, but may be only on the package insert. Again, check other resources if package inserts are not available.

e.g., Clavamox© (amoxicillin/clavulanic acid)

- May be given with or without food
- Will cross the placenta in a pregnant patient but considered safe during pregnancy
- Shake it well before using (liquid form)

The Use Of Expired Drugs (see article at end of handout)

'Shelf life' is the recommended length of time that food, drink, medicine and other perishable items can be stored, under expected (or specified) conditions, before they're considered unsuitable for sale or consumption. Most shelf life labels or listed expiration dates are used as guidelines based on normal handling of products.

Few drugs have limited drugs shelf

- Vaccines & Vitamins – especially once exposed to air
- Tetracyclines – may become toxic after expiration
- Alcohol based cough syrups – become more potent as alcohol evaporates
- Fenbendazole – may become more toxic as drug settles out of suspension

General guidelines:

- Reconstituted drugs and vitamins expire when the label says they do
- Compounded* (liquid—oral or injectable) usually expire when the label says they do
- All drugs keep longer when cool (and tablets/capsules/powders keep longer when dry)
- Drugs expire more quickly once opened, especially liquids, including IV (28 day rule)
- Liquids (oral or injectable) that change color or start to settle out should be disposed or, regardless of the expiration date
- Donated drugs that are at or past expiration can be used if they aren't vitamins, haven't been opened, haven't been exposed to temperature extremes, etc.

*****Compounding is the process of preparing drugs for a unique use. Compounding sometimes involves nothing more than crushing a pill into a powder and then mixing it into a liquid, while other types of compounding involve sophisticated scientific operations; compounding can also be practiced by taking raw components for a prescription and preparing them locally. Compounding is useful in changing the form of the drug (e.g., convert tablet to liquid); or for diluting larger human-sized drugs into smaller concentrations for smaller wildlife patients.

Testing if drug is still viable
Some labs (e.g., The Pharmacology Laboratory at the University of Tennessee, College of Veterinary Medicine; address following *References*) will test expired drugs to see if they are still effective. This may be cost-effective for large amounts of an expensive drug.

Proper Storage

- When possible, keep cool & dry
- Keep tightly sealed until used; date when opened
- Injectable drugs can be "resealed" using Parafilm™ or Tegaderm™
- Keep controlled drugs (all schedules) and potentially abused drugs under lock & key
- Some drugs need to be stored in the dark (ivermectin, Clavamox©, etc.)
- Some reconstituted drugs can be stored in aliquots and frozen (e.g., ceftazidime)

List of which oral meds should be protected from light and moisture:
http://connection.ebscohost.com/c/articles/34733412/
List of injectable drugs that should be protected from light:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3940680/

Responsible Disposal of Various Medications
Not just expired medications, but also used formalin, cleaning products, x-ray chemicals, cadavers euthanized by chemical injection, etc. Until recently, most drug disposal advice was: 'Dilution is the solution to pollution.' Better guidelines were developed in 2008:

- Example of good guidelines (NY): http://www.dec.ny.gov/chemical/45083.html
- Use Hazardous Waste Collection sites, hospitals, and incineration
- Small amounts: place in Ziploc™ bag with kitty litter
- Place inside sharps containers or inside cadavers destined for incineratin
- Disposal of controlled substances (schedules III-V) should be recorded, and these records should be kept for 2 years

The following is excerpted from: *Do Medications Really Expire?* by Richard Altschuler

Does the expiration date on a bottle of a medication mean anything? First, the expiration date, required by law in the United States, beginning in 1979, specifies only the date the manufacturer guarantees the full potency and safety of the drug -- it does not mean how long the drug is actually "good" or safe to use. Second, medical authorities uniformly say it is safe to take drugs past their expiration date -- no matter how "expired" the drugs purportedly are. Except for possibly the rarest of exceptions, you won't get hurt and you certainly won't get killed. A contested example of a rare exception is a case of renal tubular damage purportedly caused by expired tetracycline (reported by G. W. Frimpter and colleagues in *JAMA*, 1963;184:111). This outcome (disputed by other scientists) was supposedly caused by a chemical transformation of the active ingredient. Third, studies show that expired drugs may lose some of their potency over time, from as little as 5% or less to 50% or more (though usually much less than the latter). Even 10 years after the "expiration date," most drugs have a good deal of their original potency. So wisdom dictates that if your life does depend on an expired drug, and you must have 100% or so of its original strength, you should probably toss it and get a refill, in accordance with the cliché, "better safe than sorry." If your life does not depend on an expired drug -- such as that for headache, hay fever, or menstrual cramps -- take it and see what happens.

One of the largest studies ever conducted that supports the above points about "expired drug" labeling was done by the US military 15 years ago, according to a feature story in the *Wall Street Journal* (March 29, 2000), reported by Laurie P. Cohen. The testing, conducted by the US Food and Drug Administration (FDA), ultimately covered more than 100 drugs, prescription and over-the-counter. The results showed that about 90% of them were safe and effective as far as 15 years past their original expiration date.
A former director of the testing program, Francis Flaherty, noted that a drug maker is required to prove only that a drug is still good on whatever expiration date the company chooses to set. The expiration date doesn't mean, or even suggest, that the drug will stop being effective after that, nor that it will become harmful. "Manufacturers put expiration dates on for marketing, rather than scientific, reasons," said Mr. Flaherty, a pharmacist at the FDA until his retirement in 1999. "It's not profitable for them to have products on a shelf for 10 years. They want turnover."

Joel Davis, a former FDA expiration-date compliance chief, said that with a handful of exceptions -- notably nitroglycerin, insulin, and some liquid antibiotics -- most drugs are probably as durable as those the agency has tested for the military. "Most drugs degrade very slowly," he said. "In all likelihood, you can take a product you have at home and keep it for many years, especially if it's in the refrigerator." Consider aspirin. Bayer AG puts 2-year or 3-year dates on aspirin and says that it should be discarded after that. Dr. Jen Carstensen, professor emeritus at the University of Wisconsin's pharmacy school, who wrote what is considered the main text on drug stability, said, "I did a study of different aspirins, and after 5 years, *Bayer* was still excellent. Aspirin, if made correctly, is very stable.

References

Alvarado, T., M. Garner, K. Gamble, G. Levens, J. Raymond, and R. Nordhausen. 2001. Fenbendazole overdose in four Fea's vipers (*Azemiops feae*). *Proceedings of the Annual Conference of the American Association of Zoo Veterinarians*. Pp. 28-29.

Cpvh.com. 2009. Amoxicillin/Clavulanic Acid. www.cpvh.com/Pharmacy/ph6.html. Claws & Paws Veterinary Hospital: Pearland, TX.

Frazier, D.L. 2000. Avian Toxicology. *Manual of Avian Medicine* (G.H. Olsen and S.E. Orosz, eds). Mosby, Inc.: Philadelphia, PA.

Gogoi, P. 2006. The Truth About Food Expiration Dates. *Bloomberg Business.* Available from:http://www.bloomberg.com/bw/stories/2006-09-30/the-truth-about-food-expiration-datesbusinessweek-business-news-stock-market-and-financial-advice

Howard, L.L., R. Papendick, I.H. Stalis, J.L. Allen, M. Sutherland-Smith, J.R. Zuba, D. L. Ward, and B. A. Rideout. 2002. Fenbendazole and Albendazole Toxicity in Pigeons and Doves. *Journal of Avian Medicine and Surgery*. 16(3): 203-210.

Office of Research Compliance Boston University and Boston Medical Center. 2009. Conditional Use of Expired Medical Materials. http://www.bu.edu/orccommittees/iacuc/policies-and-guidelines/conditional-use-of-expired-medical-materials/

O'Rourke, K. 2004. Veterinary Drug Kills Vultures Abroad. *Journal of the American Veterinary Medical Association*. 234(8): 1238-1240.

Rosenberg, J. M., S. Schilit, and J.P. Nathan. 2008. Which oral solid medications should be protected from light and/or moisture? *Drug Topics*. 152(6): 25.

Schonwald, S. and I. M. Leviton. 2004. Sulfonamide and Quinolone Antibiotics. *Medical Toxicology,* 3rd ed. (R. C. Dart, ed.). Lippincott, Williams & Wilkins: Philadelphia, PA.

Tabaka, C. 2003. Medical Misinformation on the Internet and How it Can Harm Your Tortoise. World Chelonian Trust, http://www.chelonia.org/Articles/Medical_misinformation.htm.

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Using the NWRA Wildlife Formulary

The formulary is divided into general drug categories (analgesics, anesthetics, antidotes, antibacterials, emergency drugs, euthanasia drugs, fluids, GI/renal, nebulizing, nutritional, ophthalmics, otics, etc.

The entry for each drug is in this format:

Generic Name: The chemical name of the drug.

Symbols appearing next to the Generic Name:

& = Do not use in animals that may be eaten/hunted

* = Can be used in animals that may be eaten/hunted, but must not release until withdrawal period is over. Recommended withdrawal times for cattle have been used as a guide.

= Controlled substance; needs to be kept locked and use should be logged

% = Caution with handling or disposal (e.g., chloramphenicol)

^ = Requires special storage (refrigerate, keep dark, etc.)

Trade Name: Common commercial or brand names; these change frequently, so this list is not all-inclusive. For those drugs containing combination formulations, the composition appears in parentheses following the brand name: e.g., Droncit (praziquantel), Drontal (praziquantel/pyrantal pamoate).

Class: For antibiotics only; indicates the general classification (e.g.,aminoglycoside, macrolide, etc.).

Indications: The common uses of the drug in wildlife, as detailed by the authors or references.

Form: Only the commonly used forms of drugs are listed here. Some drugs will require modification (e.g., dilution, reconstitution or compounding) prior to use to arrive at the concentrations provided.

Dosages: Usually provided in a table and based on the species. Dosages are usually provided as a range within which the patient condition and therapeutic goals should contribute to the determination of an appropriate dose. As a rule of thumb, animals of lesser body size require progressively greater amounts of drug (due to more rapid metabolic rates), whereas animals of larger body size will require less. However, body weight alone should not be the sole criterion for calculating a drug dose; factors such as species, injuries, and stress may be considered in determining the dosage to use.

Amount: Amount of drug to be given per dose, usually listed as mg/kg of body weight

Route: The drug should only be administered by the routes specified for that species—alterations may cause harmful reactions. PO (*per os*, oral), IM (intramuscular), SQ (subcutaneous), IV (intravenous), IO (intraosseous), ICe (intracoelomic), SCa (subcarapacial), TO (topically), in drinking water, or via CRI (constant rate infusion, delivered slowly by IV).

Frequency: How often the drug should be administered based on the time that species uses to metabolize it, listed as the time between doses (e.g., q6h = every six hours, or q7d = every seven days).

Duration: Most drugs are given to effect or for a few days after desired effect (e.g., most antibiotics should be administered for at least two days after the infection has cleared completely). Some antiparasitic drugs are given for a specific duration or repeated after a set number of days in order to break the life cycle of the parasite, and some vaccines need to be repeated after a certain number of days in order for the animal to mount a complete immune response.

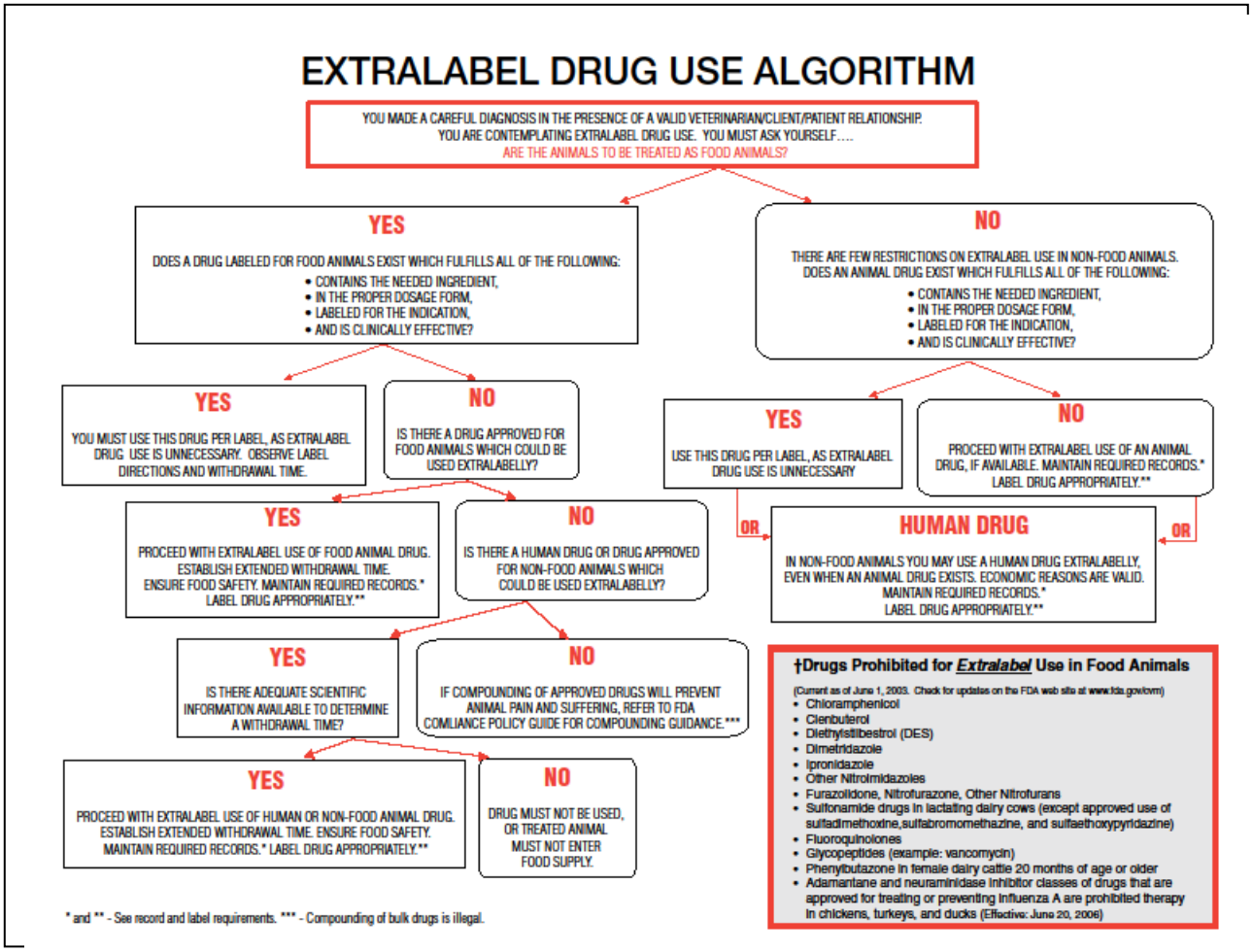
Species: Dosages are generally provided for large taxonomic groupings of mammals, birds, reptiles, or 'all species'. Whenever known, groups or species within these broader classifications are listed with specific dosages. The use of drugs in specific species or groups for which contraindications are listed (see below), or in a major grouping (e.g., 'birds') that does not appear for that drug, *is not recommended*.

Contraindications: Common known precautions, including specific species contraindications (e.g., toxic to porcupines), and concurrent disease or status contraindications (e.g., hepatic insufficiency, general debilitation, growing animals, pregnancy). Prohibited or restricted uses in food animals is also specified in this section. See 'Withdrawal Times and Prohibited Drug Use' for more information.
Pharmacology: A brief description of the drug's spectrum of activity and/or mechanism of action and when relevant, the drug's metabolism by the body.

Comments: Any additional information is provided here, including further precautions, mixture preparation, suggestions for medications that may be more appropriate (safer, more effective).

References: A list of numbers corresponding to references in the bibliography. These references provide information on specific drug dosages, mechanisms of action, drug composition, specific studies, etc.

Withdrawal Times and Prohibited Drug Use
Withdrawal times are ***approximate*** as most have not been studied or reported in native wildlife species. Food-animal withdrawal times for meat were used as a guideline for the drugs in this publication when off-label use was permitted for a specific medication. A number of medications are federally listed as "prohibited" from any off-label use; ***these drugs should not be used in any wild animal that may be hunted for food.*** Drug metabolic studies have not been done in wildlife species, so FARAD highly recommends allowing a *30-day withdrawal time for any of the listed drugs used in animals that might be hunted and consumed by humans.* See package inserts and the FARAD website for more information.



GROUP I. ***Drugs with No Allowable Extra-Label Uses in Any Food-Producing Animal Species***

- **CHLORAMPHENICOL**
- **CLENBUTEROL**
- **DIETHYLSTILBESTEROL (DES)**
- **FLUOROQUINOLONE-CLASS ANTIBIOTICS**
- **GLYCOPEPTIDES** – all agents, including **VANCOMYCIN**
- **MEDICATED FEEDS**
- **NITROIMIDAZOLES** – all agents, including **DIMETRIDAZOLE, IPRONIDAZOLE, METRONIDAZOLE** and others
- **NITROFURANS** – all agents, including **FURAZOLIDINE, NITROFURAZONE** and others

GROUP II. **Drug Classes with Prohibited ELDU or with Restricted ELDU in Food-Producing Animal Species**

- **ADAMANTANE & NEURAMINIDASE INHIBITORS:**
  - Extra-label use (ELDU) of these drugs is prohibited in poultry including chickens, turkeys and ducks in the United States. Although these drugs are not approved for use in animals in the United States, some of these drugs are used in other countries for the treatment or prevention of avian influenza in chickens, turkeys and ducks.
- **CEPHALOSPORINS**
  - ELDU of all cephalosporin antibiotics, except CEPHAPIRIN, is **restricted** in the United States.
  - ELDU restrictions differ for Major vs. Minor Food Animal Species as noted below:
    1) **Major Food Animal Species** (Cattle, Pigs, Chickens and Turkeys): ELDU is permissible only for therapeutic indications that are not included on the product label. However, ELDU of cephalosporin antibiotics is **prohibited** in all of the following situations:
       a) the intended use of the product deviates from the approved dose, treatment duration, frequency or administration route on the product label,
       b) the intended use of a product in an unapproved major species or animal production class,
       c) the intended use of the product for the purpose of disease prevention,
    2) **Minor Food Animal Species** (all species that are not major species): ELDU of cephalosporin antimicrobial agents is permitted in these species.
- **GENTIAN VIOLET**
  - use is **prohibited** in food or feed of all food-producing animal species
- **INDEXED DRUGS**
  - ELDU of these drugs is **prohibited** in all food producing animals, with some exceptions for minor-use animal species that are not used as food for humans or other animals.
- **PHENYLBUTAZONE**
  - all uses of this drug are strictly **prohibited** in female dairy cattle greater than 20 months of age.
- **SULFONAMIDE–CLASS ANTIBIOTICS**
  - ELDU of all sulfonamides and potentiated sulfonamides is **prohibited** in adult lactating dairy cattle or dairy cattle greater than 20 months of age.
  - only labeled uses of approved sulfonamides are allowed.
  - ELDU of sulfonamides in milking sheep and goats is discouraged but not prohibited.

GROUP III. ***Drugs with Special Restrictions for Grade "A" Dairy Operations***

Based upon recommendations by the National Conference on Interstate Milk Shipments (NCIMS), the FDA publishes a set of minimum standards and requirements for the production of Grade "A" milk. These standards, which are published collectively as the **Grade A Pasteurized Milk Ordinance** (Grade "A" PMO), provide applicable CFR references and can be used as an inspectional guide to cover specific operations in the dairy industry, including pasteurization equipment, packaging, quality control and record keeping requirements. Although the PMO does not have the force of regulations, it provides procedures and standards of general applicability that are acceptable to FDA. Owing to human food safety concerns, certain drugs are not to be used or not to be stored on dairy operations or fed to lactating dairy cattle. These restrictions include:

- **NON-MEDICAL GRADE DIMETHYLSULFOXIDE (DMSO)** — no use or on-site storage allowed
- **DIPYRONE** — no use allowed
- **COLLOIDAL SILVER** — no use or storage allowable
- **SYSTEMICALLY–ACTING DRUGS THAT ARE APPLIED TOPICALLY** (including **Fenthion**, **Famphur** and **Xylene**, **Phosmet**, **Levamisole** and all **ivermectins** and **avermectins**) — use of, or storage with lactating cattle medications, is a violation of Item 15r-Drug and Chemical Control

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