Law: People Are Not Cows and Off-label Prescribing Is Utterly Different

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Disclosure

- Gerald Gianutsos has no relationship with ineligible companies.

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Objectives

- *By the end of this lesson, the participant will be better able to:*
  - Discuss the characteristics and trends in off label prescribing.
  - Distinguish between off label prescribing for people and animals.
  - Describe the FDA's authority to regulate off label prescribing.

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What Will We Discuss?

- What is off-label prescribing?
- Scope of off-label prescribing/dispensing.
  - Recent examples
- Regulation
  - FDA's Role
  - Animals v People.

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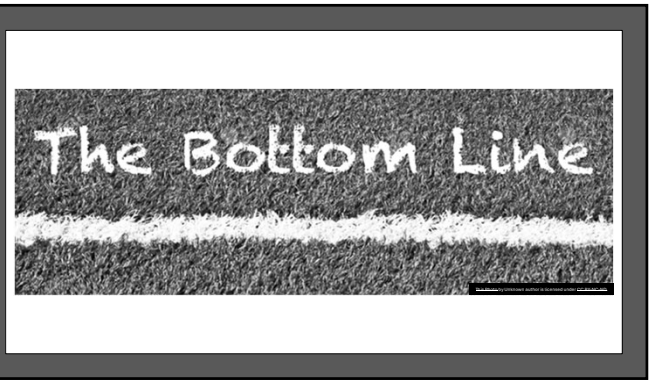

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What Is On-Label?

When a drug is approved by the FDA, it is approved for the specific indication that was the object of the clinical trial.

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Off-Label Drugs

Drug is being used in a manner that is NOT part of the FDA approval

- Not included in FDA-required drug-labelling information

https://colbertpkg.com/package-inserts/

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Types

Based on dose	Drugs given at doses other than those stated in approved product information
Based on age	Drugs prescribed outside approved age range
Based on route	Drugs administered by unapproved route of administration
Based on indications	Drugs used for indications other than those stated in approved product information
Modification of registered medication	Preparations of suspensions from capsules or tablet; Using an *oral* preparation as a topical agent

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How Common Is Off-Label Drug Use?

One in five prescriptions written today are for off-label use.

Source: Agency for Healthcare Research and Quality

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Some Populations Have Higher Use

- Pediatric (70%)
- Elderly
- Psychiatric (>30%)
- Oncology (30 – 55 %)

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Which Drugs?

- The highest rates of off-label use:
  - Anti-seizure (74% of Rxs)
  - Antipsychotics and anti-depressants (60%)
  - Antibiotics (41%)
  - Oncology
    - 13%-71% of patients received a minimum of one off-label chemotherapy
  - Biologics
- Atypical antipsychotics and antidepressants are particularly likely to be used off-label without strong evidence

Stafford RS. N Engl J Med 2008; 358:1427-1429. DOI: 10.1056/NEJMp0802107; Saiyed MM, Ong PS, Chew L. Off-label drug use in oncology: a systematic review of literature. J Clin Pharm Ther. 2017;42(3):251-258. doi: 10.1111/jcpt.12507.

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Why Are Off-Label Drug Uses Needed?

Therapeutic advances move faster than the regulatory process.

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Rationale for Off-Label Drug Use

- Certain patient populations may not typically be subjects for clinical trials and, therefore, the drug is not approved in that population, but the drug may be well known to be effective in another population with the same or milder form of a disease state
- "Drug class effect:" If a drug belonging to a particular therapeutic or pharmacological class (e.g., SSRI) has shown promise, other drugs in that class with a potentially superior therapeutic profile may be tried as well

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Off-Label Drug Use

- Two conditions may share many symptoms so that a drug effective against those symptoms may be used in the unapproved indication
  - Ex: The antiasthmatic montelukast [Singulair] for chronic obstructive pulmonary disease
- Two diseases may share a physiological link which may justify extension of a known drug to the related disorder
  - Ex: The use of the antidiabetic drug metformin to treat polycystic ovarian syndrome)
- Treatment of "orphan" condition
  - Stafford RS. Regulating Off-label Drug Use – Rethinking the Role of the FDA. *N Engl J Med*. 2008; 358: 1427-1429.

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FDA Position

The FDA recognizes that off-label drug use is accepted and necessary and regulation of this practice would interfere with the practice of medicine

"*FDA-approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient*"

FDA Draft Guidance. January 2009.
http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm

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- FDA regulates all approval and post-approval aspects of a drug product, including labelling
- But FDA does not regulate the practice of medicine
- Prescribers, therefore, may prescribe an FDA-approved drug for indications that FDA has not reviewed for safety and effectiveness
- But those uses and risks are not addressed in the labeling information (dosing, warnings about interactions with other drugs, and possible adverse events)

- https://fas.org/sgp/crs/misc/R45792.pdf

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Why Not Make Off-Label Drugs On-Label?

- Supplemental new drug application
- Usually financial
  - No incentive to seek FDA approval
  - Drug may be off-patent

- There are exceptions:
  - Minoxidil
    - Developed in 1950s as potential therapy for ulcers
    - FDA-approved for hypertension in 1979 (Loniten); hair growth noted in clinical trials
      - Dermatologists began prescribing off-label for hair loss to over 100,000 men/year in 1980s
    - FDA Approved for hair loss in 1988 (Rogaine)
    - FDA Approved as OTC drug in 1996
  - Bupropion
    - Wellbutrin for depression (1985)
    - Zyban for smoking cessation (1997)
    - Contrave (Bupropion with naltrexone) for weight loss (2014)

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Risks

Do not have the benefit of an FDA-reviewed analysis of safety and effectiveness data

Available information to support safety and effectiveness may be inadequate

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Risks

- "Some off-label uses are evidence-based and involve a scientific consensus, while some are based on anecdotal evidence or non-scientific theories."
  - Ryan Abbot, professor of law and health sciences at the University of Surrey and a professor of medicine at the University of California, Los Angeles

https://www.reuters.com/article/idUSL1N3AB1PS/

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Effect on Counseling.

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Question 1

Off label drug uses generally do not become on-label uses. What is a primary reason for this?

A. There is a financial disincentive.
B. The FDA has no readily-available mechanism to accomplish this.
C. Manufacturers do not want to distract attention from the primary use of their drug.

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Application of Off-Label Use

Examples

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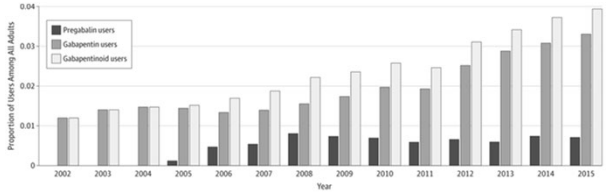

https://www.painnewsnetwork.org/stories/2018/1/2/lyrica-and-neurontin-use-triples

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Gabapentin (and Related Gabapentinoids)

- Originally approved for seizures in 1994
- Approved for treating post-herpetic neuralgia (2002), diabetic neuropathy, fibromyalgia, pain from spinal cord injury
- Used off-label for pain and also migraines, social phobia, attention-deficit disorder in children, gastric ulcers, restless leg syndrome, essential tremor, osteoarthritis, backache, insomnia, anxiety, bipolar disorder, panic attacks, hot flashes and withdrawal from cocaine and alcohol
- 83% off-label

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Gabapentin

- Use more than tripled between 2002-2015
  - Large increases in patients over 64, diabetics, and those who reported more than 2 opioid prescriptions and/or a benzodiazepine prescription
- Was aggressively promoted by manufacturer
- Limited evidence for pain relief
  - Possible risk of dependence
  - Possible increased risk of overdose among individuals concomitantly taking opioids

Johansen ME. *JAMA Intern Med*. 2018;178(2):292-294. doi:10.1001/jamainternmed.2017.7856

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Example

- Fluvoxamine (SSRI) has been promoted as a treatment for COVID-19
- Based on (limited) evidence of possible anti-inflammatory effects
- Research funded by a foundation founded by a tech entrepreneur
  - Based on results from 113 workers at a California racetrack who tested positive for COVID-19 and were offered fluvoxamine
    - None of the 65 who took fluvoxamine were hospitalized, compared with six of 48 (12.5%) who declined the drug
    - Lenze EJ, *et al*., JAMA 2020;324(22):2292-2300. https://jamanetwork.com/journals/jama/fullarticle/2773108
  - Hired PR firm and research was mentioned by *LA Times, 60 Minutes,* and *Science News*
- Offered $1 million to anyone who can identify a confounder that better explains these results

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Fluvoxamine

Posted on blog:

Describes fluvoxamine as "a small pill that transforms this destructive virus into a mild-mannered common cold"

"The fast, easy, safe, simple, low-cost treatment for COVID that has worked 100% of the time to prevent hospitalization that nobody wants to talk about"

"The mainstream media ignored it (results), so nobody knows what it is. An effective treatment for COVID is hiding in plain sight, but nobody wants to hear it."

https://www.skirsch.io/flv-works/

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Fluvoxamine

Posted on blog:

- *"If everyone talked to their doctor about taking fluvoxamine after being infected by COVID, all of data we have now very clearly shows that it would dramatically reduce the hospitalization rate, likely by a factor of 4 or more.*
- *Most doctors will not have time to review the evidence. They will stick to the tried and true and not prescribe anything until it is proven in a phase 3 trial or there is an EUA (because then they can "blame" the FDA)."*

https://www.skirsch.io/flv-works/

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Postscript

- Recent evidence suggests that fluvoxamine may reduce COVID-19 hospitalizations
  - Clinical trial in Brazil found that patients with COVID and risk factors for serious adverse effects from COVID given fluvoxamine were 32% less likely to be hospitalized compared with placebo
  - 91% reduction in death rates
  - Other smaller studies showed similar results
  - Other SSRI's?

https://www.wsj.com/articles/antidepressant-significantly-reduces-covid-19-hospitalization-11635373800?mod=djem10point

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- Ivermectin prescriptions in WEEK of 08/13/21: 88,000
- Average number of YEARLY prescriptions before COVID: 3600

- Chua et al. JAMA 2022;327(6):584

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FDA's Role

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FDA's Role

- FDA cannot regulate how prescribers use an approved drug.
- However, they can issue warnings.

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U.S. FDA
@US_FDA

You are not a horse. You are not a cow. Seriously, y'all. Stop it.

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However …

- Physicians alleged that posts interfered with their "ability to exercise professional medical judgment in practicing medicine."
- Also said their reputations were harmed by the FDA campaign because they promoted ivermectin use.
  - One physician was suspended from a hospital, while another was fired from a medical school.
- Asked court to declare posts unlawful and declare that FDA cannot issue statements or directives about how or whether health professionals should use ivermectin "off-label".
- FDA: "Such FDA actions have no legal effect and do not bind health professionals or patients."

- https://www.courthousenews.com/wp-content/uploads/2023/09/fifth-circuit-ivermectin-order.pdf
- https://thehill.com/regulation/court-battles/4184259-federal-appeals-court-revives-lawsuit-against-fda-over-covid-19-ivermectin-messaging/

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However…

- District Ct sided with FDA.
- Physicians appealed.
- Appellate Court overturned decision.
  - "FDA is not a physician. It has authority to inform, announce, and apprise — but not to endorse, denounce, or advise."
  - "Even tweet-sized versions of personalized medical advice are beyond FDA's statutory authority."
  - "The Doctors have plausibly alleged that FDA's Posts fell on the wrong side of the line between telling about and telling to."
  - Must protect physician-patient relationship from FDA interference

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Aftermath

- FDA agreed to delete Twitter, LinkedIn, Facebook and Instagram posts discouraging ivermectin's use for Covid-19.
- Also agreed to take down the 2021 consumer update "Why You Should Not Use Ivermectin to Treat or Prevent COVID-19."
- FDA said that the agency "has chosen to resolve this lawsuit rather than continuing to litigate over statements that are between two and nearly four years old."
- Also said they stand behind their position that "currently available clinical trial data do not demonstrate that ivermectin is effective against Covid-19."

https://endpts.com/fda-to-delete-you-are-not-a-horse-post-and-others-in-ivermectin-case-settlement/

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Long-Term Consequences?

What will this mean for FDA's ability to protect public health?

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Question 2

The FDA was sued for publishing a warning about the off label use of ivermectin for COVID. The basis of the lawsuit is:

1. The FDA cannot prevent physicians from prescribing a drug off-label.
2. The FDA's warning on ivermectin was erroneous.
3. The FDA overstepped its authority in publishing the warning and interfered with the doctor-patient relationship.

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Promotion

- It is illegal for drug manufacturers to directly promote or advertise a drug for any indication that the FDA has not approved
- However, information may be *communicated*
  - Must be truthful and non-misleading
  - Can respond to unsolicited requests from health care professionals
  - Can distribute independent peer reviewed article and clinical practice guidelines
  - Can support independent medical education programs

https://www.healthaffairs.org/do/10.1377/hpb20160630.920075/#:~:text=A%20drug%20is%20used%20off,is%20both%20legal%20and%20common

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Promotion

- Sometimes manufacturers overstep allowable bounds.
- Have faced significant fines (Billions).

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Veterinary Drugs

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Veterinary Drugs

- **Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA)**
  - Permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals *under certain conditions.*
    - Includes use in species not listed in the labeling.
    - Human drug.

https://www.fda.gov/animal-veterinary/guidance-regulations/animal-medicinal-drug-use-clarification-act-1994-amduca

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AMDUCA

- Before the AMDUCA was passed, it was illegal to use an FDA-approved drug in a manner that differed *in any way* from the drug's approved labeling.

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/amduca

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Necessity for Extra-Label Use

- Estimated that only 15% of animal diseases have an FDA approved animal drug.

https://www.anivive.com/learn/article/is-it-safe-to-use-human-drugs-on-animals

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Veterinary Drugs

- **AMDUCA**
  - Extralabel use is limited to circumstances when the health of an animal is threatened, or suffering or death may result from failure to treat.
  - Extralabel use to enhance production is not permitted.

https://www.fda.gov/animal-veterinary/guidance-regulations/animal-medicinal-drug-use-clarification-act-1994-amduca

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Requirement

- Extralabel use of an approved new animal or human drug must be by or on the lawful order of a veterinarian within the context of a veterinarian-client-patient relationship (VCPR).

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VCPR

- A valid VCPR is established when a veterinarian has assumed the responsibility for making medical judgments regarding the health of the animals and the need for medical treatment, and the client has agreed to follow the instructions of the veterinarian.
- The veterinarian has sufficient knowledge of the patient to initiate at least a general or preliminary diagnosis of the medical condition of the patient.
  - Veterinarian is personally acquainted with the keeping and care of the patient by virtue of a timely examination of the patient, or medically appropriate and timely visits by the veterinarian to the operation where the patient is managed.

https://www.wifss.ucdavis.edu/wp-content/uploads/2015/FDA/fdacoursefinal1/Extralable%20Drug%20Use-AMDUCA_new.pdf
https://www.avma.org/resources-tools/pet-owners/petcare/veterinarian-client-patient-relationship-vcpr#:~:text=The%20veterinarian%2Dclient%2Dpatient%20relationship%20(VCPR)%20is%20the,to%20the%20health%20of%20animals.

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Criteria

- One of the following criteria also must be met:
- No approved animal drug is available for the intended use.
- An approved animal drug is available for the intended use, but:
  - That drug does not contain the needed active ingredient.
  - That drug is unavailable in the needed dosage form
  - That drug is unavailable in the required concentration.
  - The veterinarian has found, within the context of a valid VCPR, that the drug is clinically ineffective when used as labeled.

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/amduca

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Further Differences

- Rules for ELDU differ between nonfood producing- and food-producing animals.
- One critical difference concerns approved human drugs.
  - For nonfood-producing animals, a veterinarian may prescribe or dispense an approved human drug for ELDU even if an approved animal drug is available. However, use of a drug approved for animals is preferred.
  - For food-producing animals, extralabel use of an approved human drug is prohibited if there's a drug approved for use in food-producing animals that could be used instead.

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/amduca

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Example

- Example: When treating a cow for a disorder, a drug approved for swine is available for that indication but not a drug approved for cattle.
- Must first use that drug to treat a sick cow before choosing a drug approved for humans.

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Prohibitions

- Certain drugs are prohibited from ELDU in food-producing animals.
- FDA maintains a list of those drugs.
  - Most are antimicrobials.
  - Found in 21 CFR 530.41
- Approved drugs cannot be administered in feed.

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/amduca
https://vetmed.illinois.edu/2022/08/26/pharmacists-corner-overview-of-extra-label-drug-use-in-food-animals/

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Food Animals

- FDA considers the major food-producing animal species to be cows, pigs, chickens, and turkeys.
  - However, humans legally can consume any animal as food, and many traditionally food-producing animals are kept as pets (e.g., chickens, pigs, goats, rabbits) or maintained as breeding stock.
  - Neither the FDA nor Congress has statutorily defined a food-producing animal strictly by species.
- Designation as a food-producing animal has traditionally been decided by the animal's intended purpose.

https://www.powerpak.com/course/print/123328

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Prohibitions

- Drugs prohibited from ELDU in all food animals, including horses intended for human food:
  - Chloramphenicol
  - Clenbuterol
  - Diethylstilbestrol (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
- Other medications with restrictions for ELDU in food-producing animal species:
  - Amantadine and Neuraminidase Inhibitors: ELDU prohibited in poultry including chickens, turkeys and ducks in the U.S.
  - Cephalosporins: ELDU of all cephalosporin antibiotics, except Cephapirin, is restricted in the U.S.; ELDU restrictions differ for major vs. minor food animal species
  - Gentian Violet: Use prohibited in food or feed of all food producing species
- Indexed Drugs: ELDU 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 prohibited in female dairy cattle >20 months of age
  - Sulfonamide-Class Antibiotics: Use of all sulfonamide drugs is prohibited in lactating dairy cattle, except for approved uses of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine

https://vetmed.illinois.edu/2022/08/26/pharmacists-corner-overview-of-extra-label-drug-use-in-food-animals/

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Prescription Labelling

- Name, address, and telephone number of veterinarians
- Name of clients
- Identification of animal(s) treated, species and numbers of animals treated, when possible
- Date of treatment, prescribing, or dispensing of drug
- Name, active ingredient, and quantity of the drug (or drug preparation) to be prescribed or dispensed
- Drug strength (if more than one strength available)
- Dosage and duration
- Route of administration
- Number of refills
- Cautionary statements, as needed
- Expiration date if applicable
- Slaughter withdrawal and/or milk withholding times, if applicable

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/pharmacy/prescriptions-and-pharmacies-faqs-veterinarians

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Requirements

- If a medication is prescribed for a food animal, the veterinarian must ensure that an appropriate withdrawal time is on the prescription label.
- A pharmacist should not approve a prescription for any food animal without a withdrawal time listed.
- Any party involved in processing the prescription can face legal implications if an animal makes it into the food chain with residues due to inappropriate prescribing.

https://vetmed.illinois.edu/2022/08/26/pharmacists-corner-overview-of-extra-label-drug-use-in-food-animals/

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Performance Animals

- Racehorses and racing greyhounds are subject to anti-doping standards developed and enforced by the Association of Racing Commissioners International (ARCI).
- Four drugs are banned entirely: erythropoietin, darbepoetin, oxyglobin, and hemopure.
- In addition, use of any drug that has not been approved by the FDA is prohibited in the United States.

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Compounding

- Compounding from an FDA-approved animal or human drug is legal extralabel use under AMDUCA and FDCA.
- Compounding from bulk drug substances (active pharmaceutical ingredients for human drug) may create an unapproved new animal drug and could be prohibited.

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/compounding/compounding-faq-veterinarians#:~:text=Compounding%20from%20an%20FDA%2Dapproved,Food%2C%20Drug%2C%20and%20Cosmetic%20Act
https://www.merckvetmanual.com/pharmacology/pharmacology-introduction/new-animal-drugs,-extralabel-drug-use,-compounded-drugs,-and-generic-drugs#:~:text=There%20are%20approved%20uses%20for,also%20constitutes%20extralabel%20drug%20use

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OTC Drugs

- Pharmacists may not recommend human OTCs for use in non-human patients.
- Pet owners seeking such guidance from pharmacists and pharmacy technicians should be asked for written documentation (eg, a prescription or discharge summary) establishing that a veterinarian has recommended use of a human OTC drug in their pet.
- Pet owners who have not sought veterinary evaluation should be encouraged to consult a licensed veterinarian and discouraged from self-medicating their pets.
- Many human OTC drugs are toxic to non-human species.

https://vetmed.illinois.edu/2020/12/22/pharmacists-corner-otc-toxicities/
https://www.powerpak.com/course/print/123328

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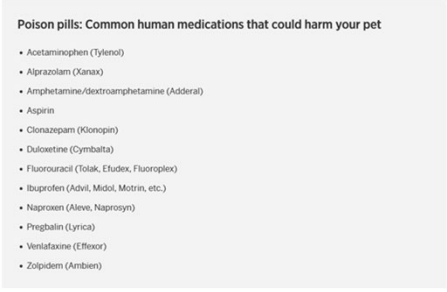

https://www.avma.org/resources-tools/pet-owners/petcare/household-hazards

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Question 3

You have a sick cow. Which of the following is correct about the type of drug that can be used for treatment?

1. Any drug approved by the FDA for human use.
2. A drug approved for use in chickens if there is no comparable drug approved for cows.
3. A drug that can be compounded by a pharmacist and added to the cow's feed.

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Reminder

Veterinarians can prescribe drugs for any species … except humans.

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Abuse

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Abuse of Veterinary Drugs

- Xylazine (#Tranq")
  - Non-opioid veterinary tranquilizer
  - Increasingly common in opioid overdose
    - Percentage of IMF-involved deaths with xylazine detected increased 276% from January 2019 (2.9%) to June 2022 (10.9%)
  - Increases duration of fentanyl and introduces euphoria.
  - Risk: abscesses, naloxone-resistant overdose.
  - Third highest incidence in U.S.: CT

Friedman J, Montero F, Bourgois P, et al. Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend.* 2022;233:109380. doi:10.1016/j.drugalcdep.2022.109380
Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022. MMWR Morb Mortal Wkly Rep 2023;72:721–727. DOI: http://dx.doi.org/10.15585/mmwr.mm7226a4

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Take Home

- OLDU in humans is common and often necessary.
- Pharmacists should recognize risks.
- FDA does not restrict OLD prescribing/dispensing in humans.
- Veterinary OLDU is restricted.
  - More restrictive in food animals.

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Thank You

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Additional Questions

What category of drugs has the highest rate of off-label use? (Prior to the pandemic.)

1. Anti-seizure.
2. Anti-depressants.
3. Antibiotics.

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Additional Questions

Why does the FDA take a hands-off view towards off-label use?

A. The FDA is not permitted to prevent manufacturers from touting an unapproved use once a drug has been approved.
B. The FDA does not regulate the practice of medicine.
C. The FDA can only act after it receives information of unintended consequences from off-label use.

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Additional Questions

When may a pharmacist recommend an OTC human drug for an animal?

A. Under any circumstances so long as it is not a food animal.
B. When there is no comparable veterinary product available.
C. A pharmacist may not recommend a human OTC drug for use in an animal.

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