LAW: Off-Label Drug Use and the Pharmacist's Role

Presented by
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For the UConn School of Pharmacy's
Henry A. Palmer CE Finale 2023

Objectives

At the conclusion of this CPE activity, participants should be able to:

1. Define the term "off-label" in terms of drug promotion, prescribing, and use.
2. Distinguish between the use of unapproved drugs and unapproved uses of FDA-approved drugs.
3. List at least two reasons why off-label drug promotion could be harmful to patients.
4. Explain whether a pharmacist has an obligation to dispense (or not dispense) a drug prescribed for an off-label use.
5. Identify potential liabilities for pharmacists who recommend off-label use of a drug.

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Disclosure

Attorney Osowiecki has no financial relationships with ineligible companies.

What does "off-label" mean?

- Off-label drug use refers to the practice of prescribing (or using) a drug for a different purpose than what the FDA approved.
  - This practice is called "off-label" because the drug is being used in a way not described in FDA-approved labeling (e.g., the "package insert" or "prescriber labeling")
- **Interesting Fact**:

  The term "off-label" is not found anywhere in the federal Food, Drug, and Cosmetic Act (FDCA)

Unapproved Use versus Unapproved Drug

- FDA recognizes that approved drugs may be prescribed for unapproved uses when a prescriber deems it medically appropriate for an individual patient
- For unapproved drugs, FDA's general position is that all drugs must be shown to be safe and effective for their intended use through one of FDA's drug approval processes
  - FDA allows unapproved drugs in limited circumstances:
    - When there are shortages of an FDA approved drug
    - Healthcare professionals rely on the drug to treat serious medical conditions where there is no FDA-approved drug for treatment
    - The drug is subject to an open drug efficacy study implementation (DESI) program proceeding

FDA's Authority to Regulate Off-Label Promotion

- FDA's authority to regulate off-label promotion draws from the FDCA's prohibitions against introducing an "unapproved new drug" or a "misbranded" drug into interstate commerce.
- If a company promotes a drug for a use that is not within the FDA-approved labeling, the FDA may deem it to be a "new drug" because it is not generally recognized as safe and effective (GRASE) "for use under the conditions prescribed, recommended, or suggested in the labeling thereof."
- The definition of "new drug" requires that the **intended** use be evident in the "labeling" of the product.

Examples of Unapproved Uses

Off-label uses can include, but are not limited to:

- When a medication is used for a condition that it is not approved to treat
- When a medication is dosed differently than what has been approved
- Treating children with a medication that has been approved for use in adults only

Providers' perspective on off-label uses

- Freedom to make evidence-based drug therapy decisions consistent with patient-care need is important
- Corresponding responsibility: if using a product for an indication not in the approved labeling, clinician must be well-informed about the product

Compounding

THOUGHT QUESTION:

Does compounding have any relationship or similarities to off-label drug use?

Concerns about pharma off-label promotion

- Information is more promotional than objective, potentially misleading providers and patients
- Expansion of use in broader groups of patients not included in clinical studies, with greater risk of harm because evidence of effectiveness and safety is lacking
- High risk of more patients exposed to side effects, drug-drug interactions, ineffective therapy
- Decreased incentive for manufacturers to conduct controlled studies about toxicity and efficacy

Off-Label Promotion by Pharma (2009-2012)

United States v. Caronia

In 2009, pharma sales rep *criminally* convicted for Xyrem off-label promotion

- FDA said: criminal conviction protects integrity of drug approval process
  - But FDA allowed manufacturers to provide some off-label information
  - And FDA had guidance on disseminating peer-reviewed reprints, sponsoring educational programs, and responding to unsolicited requests for off-label information

2012 - Conviction overturned (2nd Circuit):

"*we construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns*"

- Court reasoned that: FDCA does not prohibit off-label use by prescribers and FDA recognizes off label use, therefore, "the free flow of information" from manufacturers does not affect the integrity of the drug approval process

Off-Label Promotion by Pharma (2015-Present)

Amarin Pharma, Inc. v. United States FDA

- In 2015, Amarin challenged FDA's restrictions on off-label promotion of Vascepa (icosapent ethyl)
  - While drug was in approval process, Amarin wanted to provide prescribers with reprints of study results
  - FDA threatened prosecution for misbranding
- In 2016, Court (SDNY) found that Amarin made "truthful and non-misleading statements" to prescribers

"*Where the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under Caronia, cannot be the act upon which an action for misbranding is based.*"

Sales Representatives' Statements?

"Although the FDA cannot require a manufacturer to choreograph its truthful promotional speech to conform to the agency's specifications, there is practical wisdom to much of the FDA's guidance, including that a manufacturer vet and script in advance its statements about a drug's off-label use. A manufacturer that leaves its sales force at liberty to converse unscripted with doctors about off-label use of an approved drug invites a misbranding action if false or misleading (e.g., one-sided or incomplete) representations result. *Caronia* leaves the FDA free to act against such lapses. [(August 7 Order at 53.)]" Amarin Pharma, Inc. v. FDA (USDC SDNY 2016)

Salier v. Walmart. Inc., No. 22-CV-0082 (PJS/ECW) (D. Minn. Aug. 19, 2022)

- In October 2021, Plaintiffs (in Minnesota) became ill with COVID-19. Treating physician (in Missouri via telemedicine) prescribed ivermectin & hydroxychloroquine.
- Walmart and Hy-Vee pharmacists refused to fill the prescriptions based on corporate policy and their professional judgment
- Plaintiffs sued alleging:
  - Violation of "common law right to self-determination"
  - Intentional infliction of emotional distress
  - Tortious interference with "contract" because refusal to fill impeded prescriber's performance of obligations to provide "medical treatment to the best of [prescriber's] knowledge, skills, ability, and experience."
- Case dismissed August 19, 2022
- Affirmed on appeal to 8th Circuit August 2023

Mifepristone and Misoprostol for Early Pregnancy Loss and Medication Abortion

Honor MacNaughton, MD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Massachusetts; Tufts University School of Medicine, Boston, Massachusetts
Melissa Nothnagle, MD, MSc, Natividad Family Medicine Residency, Salinas, California; University of California San Francisco School of Medicine, San Francisco, California
Jessica Early, MD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Massachusetts; Tufts University School of Medicine, Boston, Massachusetts

Medication regimens using mifepristone and misoprostol are safe and effective for outpatient treatment of early pregnancy loss for up to 84 days' gestation and for medication abortion up to 77 days' gestation. Gestational age is determined using ultrasonography or menstrual history. Ultrasonography is needed when gestational dating cannot be confirmed using clinical data alone or when there are risk factors for ectopic pregnancy. The most effective regimens for medication management of early pregnancy loss and medication abortion include 200 mg of oral mifepristone (a progesterone receptor antagonist) followed by 800 mcg of misoprostol (a prostaglandin E, analogue) administered buccally or vaginally. Cramping and bleeding are expected effects of the medications, with bleeding lasting an average of nine to 16 days. The adverse effects of misoprostol (e.g., low-grade fever, gastrointestinal symptoms) can be managed with nonsteroidal anti-inflammatory drugs or antiemetics. Ongoing pregnancy, infection, hemorrhage, undiagnosed ectopic pregnancy, and the need for unplanned uterine aspiration are rare complications. Clinical history, combined with serial quantitative beta human chorionic gonadotropin levels, urine pregnancy testing, or ultrasonography, is used to establish complete passage of the pregnancy tissue. (*Am Fam Physician*. 2021;103(8):475-480. Copyright © 2021 American Academy of Family Physicians.)

U.S. FOOD & DRUG ADMINISTRATION

April 27, 2023

Lemrey (Al) Carter, MS, PharmD, RPh
Executive Director
National Association Boards of Pharmacy
1600 Feehanville Drive
Mount Prospect, IL 60056

Dear Dr. Carter,

In consideration of several inquiries received, we wish to clarify for state pharmacy regulators that as of today, April 27, 2023, the FDA-approved drugs Wegovy and Ozempic continue to be listed on the FDA Drug Shortage website. If a product is listed on the FDA Drug Shortage website, we still consider the product to be in shortage unless it states that it is resolved. FDA works closely with manufacturers to confirm the accuracy and appropriateness of information before posting publicly on its website(s).

As you know, depending on the circumstances, compounded drugs can be made and distributed with fewer restrictions when the drug appears on FDA's drug shortages list. Please find more information on drug compounding and drug shortages on FDA's website.

We also wish to ensure you are aware that the active pharmaceutical ingredient in Wegovy and Ozempic is semaglutide in its base form. We are aware that in some cases compounders may be using salt forms of semaglutide, including semaglutide sodium and semaglutide acetate. We are not aware of any basis for compounding a drug using these semaglutide salts that would meet federal law requirements that limit the types of active ingredients that can be used in compounding.

Please let us know if you have additional questions. Thank you.

Sincerely,

F. Gail Bormel, RPh, JD
Director
CDER Office of Compounding Quality and Compliance
frances.bormel@fda.hhs.gov

Likely Pharmacist Encounters with Off-Label Uses

AHRQ estimates that 20% of all prescriptions dispensed are for off-label use

- Community pharmacy dispensing
  - Off-label use may (or may not) be evident – examples include:
    - beta-blockers for migraine prophylaxis
    - antidepressants for pain control
    - oral contraceptives for premenstrual disorders
- Hospital / Clinical Pharmacy Review
  - Peer reviewed study
- Research / Academia / Pharma
  - New uses for old drugs: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2203255/pdf/bcp0064-0563.pdf

How Does A Pharmacist Know It's Off-Label Use?

- Patient discloses condition being treated
- Pharmacist confirms with prescriber or use is evident in prescriber's directions
- Pharmacist recommends the off-label use to a prescriber

Legal Implications for Pharmacists

- Professional judgment is key
  - No obligation to dispense for an off-label drug if professional judgment is that it could cause patient harm or be ineffective
  - But do not "defame" the prescriber to the patient
- Dispensing pharmacist has no obligation to verify the condition being treated
  - Knowledge of the patient or condition being treated could impute duty to inquire further, ask for supporting documentation from prescriber
- Informed consent / shared decision-making is a consideration
- No known duty to report off-label use to enforcement agencies
  - MedWatch
  - Licensing authorities
- If recommending an off-label use to a prescriber, know the product and the evidence-based support for the use

Extralabel Drug Use (ELDU) In Animals

- Veterinary prescribing is regulated in a manner similar to human prescribing
- Instead of "off-label" drug use, the FDA's defined term is "extralabel use"
- Extralabel use in animals is limited to when
  - the health of an animal is threatened or
  - suffering or death may result from failure to treat
- Extralabel use in food-producing animals is subject to additional specific conditions

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Compounding for Animals

[21 CFR 530.13]

Animal drug compounding from active pharmaceutical ingredients is not permitted.

- Compounding must be
  - by a veterinarian, or a pharmacist on the order of a veterinarian
  - from approved animal or human drug
  - When there is no approved animal or human drug in an available dosage form and concentration that could appropriately treat the condition
    - If for a food-producing animal, a human drug is not permitted if an approved animal drug could be used
  - Performed with adequate procedures and processes to ensure safety and effectiveness of compounded product
  - On a scale commensurate with established need
  - In accordance with all relevant State laws

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Labeling of Compounded Drugs Used for Animals

[21 CFR 530.12]

- If dispensed by a veterinarian, must include veterinarian's name & address
  - If prescription/order is dispensed by a pharmacy, name & address of pharmacy, and name of prescribing veterinarian
- Established name of the drug.
  - If formulated from more than one active ingredient, established name of each ingredient
- Directions for use, including
  - Class/species/identification of animal
  - Dose
  - Frequency
  - Route of administration
  - Duration of therapy
- Any cautionary statements
- Veterinarian's specified withdrawal, withholding, or discard time for any food derived from the treated animal (if food producing)

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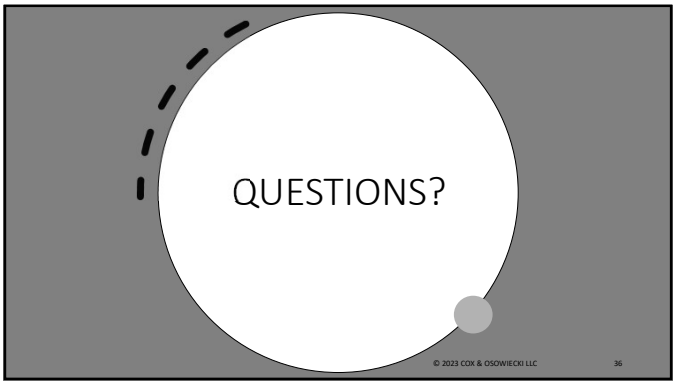

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