

# What are the Legal Issues Regarding the Use of Off-label Drugs?

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## STATEMENT OF NEED

Because ocular injections are often used in an off-label setting, it is imperative that physicians consider associated complications and the importance of informed consent. Surgeons must also understand what constitutes an off-label use of a drug and what the role of the Food and Drug Administration (FDA) is in relation to the practice of medicine.

## TARGET AUDIENCE

This activity is designed for retinal specialists and other ophthalmologists.

## LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- Identify examples of the use of off-label drugs in an ophthalmic setting;
- Discuss the four main issues with regard to off-label drug use;
- Cite key factors in chart documentation, in the setting of off-label drug use; and
- Name some issues with regard to coverage and reimbursement for the off-label use of medications.

## METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions. This test is available exclusively online, at [www.CMEToday.net](http://www.CMEToday.net). Once you register and log in, you can take the test, get real-time results, and print out your certificate. Please e-mail [ckoury@bmctoday.com](mailto:ckoury@bmctoday.com) or call 484-581-1821 if you have any questions or technical problems with the Web site.

Upon completing the activity and achieving a passing score of  $\geq 70\%$  on the self-assessment test, participants can print out a CME credit letter awarding *AMA/PRA Category 1 Credit*.™ The estimated time to complete this activity is 1 hour.

## ACCREDITATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *RETINA TODAY*.

The Dulaney Foundation designates this educational activity for a maximum of 1 *AMA/PRA Category 1 Credit*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

## DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services that relate to the content of their presentation/material or the commercial contributors of this activity; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

## FACULTY CREDENTIALS

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## FACULTY DISCLOSURE DECLARATIONS

Dr. Williams is a paid committee member and policy holder of the Ophthalmic Mutual Insurance Company.

## INTRODUCTION

What constitutes off-label drug use? Clearly it is use that is not described in the official FDA label. To further understand this concept, it is important to understand what the FDA drug label involves.<sup>1</sup>

## OFF-LABEL DRUG USE

Drug labels are disease specific, therefore if the agent is used to treat a disease that is not specified in the label, then the agent is being used off label. Additionally, any change to the approved dose, frequency or route of administration would constitute an off label use. Most drugs are approved for use in adults only, so pediatric use would also constitute an off-label use.

As we all know, ophthalmology is replete with the use of off-label therapies. Examples include the use of intravitreal antibiotics for the treatment of endophthalmitis, the use of antimetabolites for glaucoma, the

use of peri- and intraocular steroids, the use of immunosuppressives for uveitis, and photodynamic therapy for nonpredominantly classic age-related macular degeneration lesions, and most recently the use of bevacizumab intravitreal injection (Avastin; Genentech, San Francisco).

**FDA approval status does not define appropriate medical practice. In fact, the FDA does not regulate medical practice at all.**

A variety of factors came together, including availability, convenience, and cost, to create a perfect storm for bevacizumab. The publicity surrounding this agent awoke ophthalmologists to the issues of off-label drug usage, and furthermore awoke payers and regulators to the frequency of off-label drug use among ophthalmologists.

There are four major issues with regard to off-label use:

- Patient selection,
- Risk management,
- Regulatory, and
- Billing/coding/coverage.

## PATIENT SELECTION

We all recognize that FDA approval status does not define appropriate medical practice. In fact, the FDA does not regulate medical practice at all. Physicians decide what is appropriate medical practice for each patient, but we do so within the constraints of what is known as the standard of care.

According to the FDA Web site: "Good medical practice and the best interests of the patient require that physicians use legally available drugs ... according to their best judgment. If physicians use a product off label, they have a responsibility to be well informed about the product ... use firm scientific rationale and sound medical evidence.

This appears to be an endorsement from the FDA about the use of off-label drugs. The problem with off-label use is one of risk management.

## RISK MANAGEMENT

The use of off-label drugs combined with an adverse outcome is a potential malpractice disaster. A disaster that is akin to blood in the water for lawyers.

The key to managing this risk—and it can only be managed not eliminated—is informed consent.

Informed consent is a process, not a form. Within the off-label context, we must discuss with patients the off-label status of the proposed therapy and potential risks. We should consider using a drug-specific consent form, and very importantly, we must document why and how the decision was made to not use FDA or Centers for Medicare and Medicaid Services (CMS) approved therapies.

**Off-label drug use may in fact constitute the current standard of care, and in some situations, failure to provide or at least discuss off-label therapy may be malpractice.**

Off-label drug use may in fact constitute the current standard of care, and in some situations, failure to provide or at least discuss off-label therapy may be malpractice. An obvious example here is intraocular antibiotics for endophthalmitis. It is understandable if many physicians feel as if they are placed in a difficult situation, where they are damned if they do and damned if they don't.

The importance of chart documentation cannot be overemphasized. Surgeons should document:

- The decision-making process, including previous treatments and diagnostic studies;
- The informed consent discussion and off-label status;
- The dose and lot number of the off label drug, and
- Discharge and follow-up instructions.

Specific bevacizumab-related risk management as recommended by the Ophthalmic Mutual Insurance Company (OMIC) would include avoid treating patients with a high risk cardiovascular profile, use bevacizumab-specific informed consent (available at [www.omic.com](http://www.omic.com)), and being sure to provide the patient adequate time to come to a decision.

## REGULATORY ISSUES

Regulatory issues refer to, primarily, the difference between investigation and medical practice. Medical practice is the therapeutic relationship between a physician and an individual patient. Investigation implies a scientific inquiry about a treatment and requires an institutional review board (IRB) approval.

Any formal study requires an investigational new drug application (IND).

An IND is required when conducting an investigation that is intended to change the FDA label or change the risk profile of an agent. A change in risk profile might be due to a change in the dosage or the route of administration of a drug. IND applications for studies performed by physicians are available from the FDA Website. This may be required by your local IRB. While this is a tedious process, it is certainly doable.

It is important to note that some courts have held that a violation of FDA regulations is negligence per se. This has important malpractice implications, and in some cases, even criminal implications.

## COVERAGE

What is the policy of CMS regarding off-label drugs? In the Medicare Benefit Policy Manual, Ch 15, Sec 50.4.2: "FDA-approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature, and/or accepted standards of medical practice."

This appears to be an endorsement of off-label use by CMS.

**Specific bevacizumab-related risk management as recommended by the Ophthalmic Mutual Insurance Company are available at [www.omic.com](http://www.omic.com).**

There are now 48 states covering intravitreal bevacizumab. Additionally, the American Academy of Ophthalmology (AAO) and the American Society of Retinal Specialists (ASRS) support the use of bevacizumab. AAO and ASRS have been forceful and articulate advocates for access to this therapy. This does not, however, constitute an endorsement of bevacizumab. Rather, we believe it should be left up to the physician's judgment when use of this drug is appropriate.

The AAO has also contacted national CMS teams about coverage for bevacizumab. It has found that there is insufficient evidence to pursue a national coverage determination.

The retinal community has a responsibility to demonstrate the safety and efficacy of bevacizumab and other off-label drugs.

So what do surgeons do today? Is important that you contact your carrier for the details of their off-label coverage policy. If no coverage policy exists, you must use Advance Beneficiary Notice as outlined by your carrier.

Concerning coverage, the retinal community has a

responsibility to demonstrate the safety and efficacy of bevacizumab and other off-label drugs. We need to be the ones to provide adequate supporting data via peer-reviewed publications and appropriately constructed clinical trials.

Off label therapies often constitute an accepted standard of care, but they require understanding of the legal and regulatory implications. So at the present time, with the use of off-label drugs, for physicians and patients, its buyer beware. ■

1. Williams G. Legal issues regarding off-label drug use. Presented at Retina 2006: Emerging New Concepts, held in conjunction with the American Academy of Ophthalmology annual meeting. Nov. 10-11, 2006. Las Vegas.

## CME QUESTIONS

To answer these questions online and receive real-time results, you must visit [www.CMEToday.net](http://www.CMEToday.net).

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E-mail [ckoury@bmctoday.com](mailto:ckoury@bmctoday.com) if you have any problems accessing the site or taking the test online.

1. Which of the following constitute off-label drug use, according to the activity?
  - a. administration of a drug approved for adult patients to children
  - b. administration of a higher dose of a drug than listed on the label
  - c. using an agent for a different disease than that listed on the label
  - d. all of the above
2. The FDA DOES NOT regulate medical practice.
  - a. true
  - b. false
3. The use of which of the following agents in an off-label manner is NOT discussed in the activity as common among ophthalmologists.
  - a. intravitreal antibiotics
  - b. oral contraceptives
  - c. antimetabolites
  - d. bevacizumab
4. The FDA and the CMS DO NOT advocate off-label usage of drugs.
  - a. true
  - b. false
5. With regard to the importance of chart documentation to back up the use of off-label drugs, which item was NOT discussed?
  - a. informed consent
  - b. dose and lot number of the drug
  - c. name and location of supplier/compounding pharmacy
  - d. discharge and follow-up instructions
6. There is NO NEED to use a specific bevacizumab-related risk management strategy.
  - a. true
  - b. false
7. The CMS DOES NOT reimburse for any agents that are administered in an off-label manner.
  - a. true
  - b. false
8. In many cases, off-label administration of an agent constitutes the current standard of care.
  - a. true
  - b. false
9. How many states currently reimburse for intravitreal bevacizumab, according to the activity.
  - a. none
  - b. 2
  - c. 48
  - d. 16
10. What steps can the retinal community take to demonstrate the safety and efficacy of off-label drugs?
  - a. participate in peer-reviewed publication of data
  - b. participate in appropriately constructed clinical trials
  - c. conduct physician-sponsored trials
  - d. all of the above