



## Physicians' liability for off-label prescriptions

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It is estimated that between 40 and 60 percent of all prescriptions written in the United States are for off-label uses. Off-label uses are common, especially for treating cancer, AIDS, pediatric conditions and rare diseases. Because the practice is common, and in many cases necessary, physicians must consider how prescribing drugs for uses not recommended by the manufacturer—and not approved by the U.S. Food and Drug Administration—could increase their exposure to malpractice liability.

### Off-label vs. research

A common misconception among patients and non-physicians is that any time a physician prescribes a drug for a use that is not approved by the FDA, the physician is essentially conducting experimental research on the patient. The distinction between off-label use and research is important because the FDA closely regulates the sale, manufacture and labeling of drugs. Such regulation includes the development and clinical investigation of new drugs. Clinical investigation of drugs on human patients requires obtaining an Investigational New Drug exemption from the FDA prior to beginning a study, as well as close oversight by institutional review boards. Such studies must generally comply with well-developed protocols to protect both the patient's

safety and to evaluate the drug's safety and efficacy. The FDA's focus is primarily on the IND process and protection of human subjects being treated in clinical trials. The FDA does not, however, regulate the practice of medicine, and physicians are allowed to prescribe approved drugs for off-label uses as long as such prescriptions do not qualify as "research."

It is not always clear whether a physician's prescription of a drug for off-label use is experimental research. Perhaps the most basic test for whether an off-label use qualifies as experimental research is to focus on the physician's motivations and goals in prescribing for an off-label use. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research notes:

"The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called 'experimental' when the terms 'experimental' and 'research' are not carefully defined. For the most part, the term 'practice' refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. *The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals* [emphasis added]. By contrast, the term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually

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described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

"When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental,' in the sense of new, untested, or different, does not automatically place it in the category of research."<sup>1</sup>

If a physician's use of a drug qualifies as experimental research, the physician has an increased risk of professional discipline and civil liability if such experimental use does not comply with the safeguards and oversight of a formal study carefully designed to monitor

device was not approved for use at the precise location of the spine at which it was inserted. The *Brenneman* court found that, although the artificial disk was not FDA-approved for the specific procedure in which it was used, there was enough evidence to conclude that it was not used experimentally. Among the evidence on which the court relied in reaching its conclusion was that the allegedly experimental procedure was widely performed in Europe and was an easier procedure than that for which the device was expressly approved.

Although there is no single checklist that physicians can follow to insulate themselves from claims that a prescribed off-label use is experimental, the *Brenneman*

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the drug's safety and effectiveness. As a general rule, if there is any element of research in an activity (i.e., any motivation beyond diagnosing or treating an individual patient), that activity should undergo review to determine the need to include steps/procedures for the protection of human subjects.

As demonstrated in a recent medical device malpractice case, *Bax Global Inc. v. Brenneman*, 2007 Ohio 695 (Ohio Ct. App., 2007), a physician may help avoid professional liability when prescribing approved drugs for off-label uses if he or she puts the patient's interests first and can point to sound scientific and clinical data that support the off-label use in question. In *Brenneman*, the plaintiff alleged malpractice and argued that the physician's insertion of an artificial disk into her spine was an experimental use because the already FDA-approved

case shows that physicians may take precautions to reduce the potential for success of such claims. As discussed below, whenever a physician prescribes a drug for off-label use, it should be based on: (1) the doctor's own expert medical judgment; (2) peer-reviewed articles reflecting sound scientific evidence; (3) documented medical practice; (4) if possible, the opinions of the physician's local colleagues; and (5) a desire to directly benefit the patient for whom it is prescribed.

### Malpractice liability

If a patient brings a malpractice claim against a physician who prescribes a drug for an allegedly improper off-label use, the two most likely causes of action are the physician's failure to obtain informed consent and general negligence. Both of these causes of action are discussed below.

### Informed consent

The doctrine of informed consent means that a physician must present the patient with material information about proposed treatments and their alternatives, and about the risks and potential benefits of the alternatives, then allow the patient to decide which course of action to pursue. In the United States, each state establishes its own test for determining whether information is material, but the prevailing standard in most states is the "reasonable physician" standard. This standard focuses on whether a reasonable physician would provide the information at issue, with the judge or jury usually deciding the matter based on conflicting testimony by the parties' medical experts. An alternative "reasonable patient" standard is also gaining traction among the states and requires a judge or jury to determine whether a reasonable patient would have regarded the information as important. In addition to these standards, a few states have adopted a more subjective "actual patient standard," which tends to focus on what the individual patient actually believed.

In applying the doctrine of informed consent to off-label drug prescription, many courts have held that physicians do not have to disclose to patients that a proposed use is off-label. For example, in *Klein v. Biscup*, 109 Ohio App. 3d 855 (Ohio Ct. App., 1996), another medical device case, the plaintiff brought an informed consent claim against a physician who surgically implanted a medical device in her spine without telling her the treatment was an off-label use of the device. After suffering health problems following surgery, the plaintiff alleged, among other things, that the physician had not obtained her informed consent because he did not notify her that the device's use was off-label. In rejecting the plaintiff's claim, the *Klein* court held:

"The decision whether or not to use a drug for an off-label purpose is a matter of medical judgment, not of regula-

tory approval. By analogy, the off-label use of a medical device is also a matter of medical judgment, and as such, subjects a physician to professional liability for exercising professional medical judgment. Off-label use of a medical device is not a material risk inherently involved in a proposed therapy which a physician should have disclosed to a patient prior to the therapy.”(109 Ohio App. 3d at 864)

The result in *Klein* and other cases like it reflect what many commentators consider to be common sense:

“The bare fact of off-label use of a device or drug carries with it no medical information, either express or implied. While patients might have some assurance that uses actually appearing on labeling are safe and effective, they cannot imply from a label’s silence that a particular use recommended by their physician is unsafe, risky, novel, or untried. ... There is no duty obligating a physician to discuss FDA regulatory status of products being used for a particular treatment because FDA regulatory status is not a risk, benefit, or alternative of medical treatment, nor does a product’s legal status affect the nature of the treatment.”<sup>2</sup>

Other commentators have criticized courts’ usual treatment of the issue as incomplete: “Off-label status does mean that the use lacks the same assurances of safety and efficacy as an approved indication. Arguably this is something that the patient ought to be told.”<sup>3</sup>

In general, the more information physicians provide patients about alternative therapies or treatments and their risks and benefits, the less likely it is that patients will successfully assert that the physician failed to provide adequate information. And although courts have not widely held that the doctrine of informed consent requires physicians to tell their patients when a drug is being prescribed for an off-label use, doing so may add an extra level of protection against a potential finding that a physician did not obtain a patient’s informed consent.

## Negligence

Negligence is the most common basis upon which patients bring malpractice lawsuits against physicians. The plaintiff in a negligence case has the duty to prove all four elements of a negligent malpractice claim: (1) The physician owed the plaintiff a duty to act reasonably; (2) The physician breached that duty; (3) The plaintiff suffered actual harm; and (4) The harm was proximately caused by the breach of duty. Under a cause of action based on negligence, the duty of care

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the plaintiff must establish is the same level of care provided by physicians in circumstances similar to the defendant physician. In other words, a plaintiff must prove that the physician’s care departed significantly from the reasonable care delivered by hypothetical similarly situated physicians. In these cases, courts usually look to the standard of care established by similarly situated physicians in the surrounding area and communities in which a physician practices.

Physicians defending against a negligent malpractice claim may take comfort in knowing that simply prescribing a drug for an off-label use is generally viewed as not establishing a presumption that they acted negligently. Plaintiffs may recover in off-label medical malpractice cases if it can be established that a physician’s off-label prescription deviated from an acceptable and prevailing standard of practice. One court summed up this concept by stating: “A physician is free to use a medical device for an off-label purpose, if, in the physician’s medical judgment, he or she believes that use of the device will benefit the patient. Because the off-label use of a [device] is a matter of medical judgment, a physician may be

subject to medical malpractice liability for the exercise of that judgment.”<sup>4</sup>

In *Richardson v. Miller*, 44 S.W.3d 1 (Tenn. Ct. App., 2000), a woman and her husband brought a negligent malpractice action against the woman’s attending physician, claiming that he violated the standard of due care by using terbutaline sulfate off-label during her labor. Although terbutaline was approved by the FDA only for the treatment of bronchial asthma, physicians commonly used it to help delay labor by relaxing the uterine

muscles. Terbutaline may be taken orally or subcutaneously via a pump that inject small amounts of the drug. The defendant physician had limited experience with the terbutaline pump prior to using it with his patient. The plaintiffs alleged that as a result of the administration of terbutaline during her labor, the woman suffered a major heart attack, resulting in permanent heart damage. The physician’s use of terbutaline was off-label. At trial, the court granted the physician’s motion to exclude all references made to the off-label use of terbutaline, including the drug’s listing in the *Physician Desk Reference* and its package insert. On appeal, however, the Tennessee Court of Appeals held that the trial court had committed reversible error by excluding this evidence. The court found that information regarding the off-label nature of a drug is essential in helping to establish the standard of care against which the defendant should be judged. The physician failed to abide by the warnings issued by the FDA, cautioning against the use of a terbutaline infusion pump in the treatment of pre-term labor. Thus,

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the appellate court found that the lower court's decision to exclude evidence on the dangers of off-label use of terbutaline "materially hampered" the plaintiff's ability to prove her medical malpractice claims against the defendant. The court vacated the lower court verdict and remanded the case for a new trial.

The *Richardson* case is an excellent example of how courts will hold physicians responsible for information on the use of a drug even if it is not contained in the manufacturer's label or accompanying information inserts. As with any negligent malpractice action, a physician will be better able to defend against a malpractice claim for off-label use of a drug when scientific evidence exists to support the course and manner of the administered treatment. The American Academy of Pediatrics suggests that physicians consider the following when prescribing drugs for off-label uses: (1) whether the drug has been approved by the FDA; (2) whether the off-label use

has been subjected to objective scientific testing and has been approved in at least two peer-reviewed articles; (3) whether the off-label use is medically necessary to treat a specific condition; and (4) whether the off-label use is not experimental.

### Conclusion

Prescribing drugs and medical devices for off-label use can be a source of increased liability for physicians when such use falls short of patients' expectations—but it need not be. Physicians may give themselves additional protection against malpractice claims by making sure that their prescriptions for off-label uses are: (1) made with the patient's knowledge that a drug is being prescribed for an off-label use; (2) principally motivated by a desire to diagnose, treat and directly benefit the patient for whom a drug is prescribed; (3) based on the doctor's own expert medical opinion; (4) supported by reputable peer-reviewed literature reflecting sound scientific evidence; and (5) generally sup-

ported by the opinions of the physician's local colleagues. **H**

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