Ch. I-46 Off-Label Use

James Szalados, MD, Esq

ISSUE: You prescribe a medication that is not approved by the manufacturer for the clinical indication that you are treating. What should you be aware of?

The relatively common practice of prescribing a pharmaceutical for an unapproved indication is defined by the US Food and Drug Administration [FDA] as 'off-label' prescribing. Approved indications are defined for each pharmaceutical product by the FDA based on the manufacturer's drug development data and through the FDA drug approval process. The FDA drug approval standard is based upon the legislatively defined and therefore mandatory dual standards of safety and efficacy which are established through the pre-clinical and clinical testing stages of drug development. Once clinical testing has established that a drug is safe and efficacious for the indications for which it has been tested, the data is submitted to the FDA. The FDA reviews that data, and, if satisfied, the drug may proceed to marketing. FDA approval allows the manufacturer to market that drug only for certain uses, treatments, and indications, all of which must be indicated on FDA-approved labeling. The FDA defines 'labeling' to include all informative materials which accompany the drug; including, but not limited to, the package insert.

Although manufacturers are statutorily prohibited from directly marketing a drug for any use other than the FDA approved indication(s) as defined in the product's labeling, the FDA does not have the legal authority to regulate the practice of medicine, and the physician may prescribe any drug 'off label' according to his or her own best judgment. In *Buckman* the U.S. Supreme Court, in the context of medical devices, observed that "'off-label' usage … is an accepted and necessary corollary of the FDA's mission to regulate … without directly interfering with the practice of medicine."

Off-label prescribing is perhaps most commonly encountered in the specialties of pediatrics (since relatively few older drugs have been clinically tested directly in children), oncology, psychiatry, and cardiology. The Food and Drug Administration Modernization Act of 1997 created an exception to the prohibition on direct off-label marketing by manufacturers in that manufacturers are now able to provide medical practitioners with off-label information only in response to an unsolicited request from that practitioner regarding data supporting that off-label use. Manufacturers cannot promote off-label uses or otherwise induce practitioners to use a drug off-label. In 2004, Pfizer was prosecuted for inducing physicians to prescribe the drug Neurontin for unapproved indications and was fined $430 million.

Off-label use is frequently an indirect venue for expansion of drug efficacy data when 'off label' use generates written case reports, future experimental protocols, and may even prompt the manufacturer to amend the drug's labeling to make that 'off-label' use an accepted indication. A Tennessee appellate court observed in that: "[b]ecause the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment," and went on to state that "[i]n some circumstances, an off-label use of a particular drug or device may even define the standard of care." However, off-label prescribing must not be used for the purposes of research.

The distinction between therapy and research lies in the prescriber's intent: if the primary intent is patient benefit then the intervention is considered therapeutic and lies within the practice of medicine; however, if the primary intent is to test a hypothesis, gather data, or publish findings, then the intervention is likely to be considered an experiment.

The fact that neither the FDA or drug manufacturers may engage in the practice of medicine also shifts liability onto practitioners who exercise professional judgment in prescribing practice.

The "learned intermediary doctrine" is a well-accepted defense doctrine primarily used by pharmaceutical and device manufacturers in defense of manufacturing liability tort claims. The doctrine essentially states that a manufacturer of a medical

product satisfies the requisite duty of care when that manufacturer provides the necessary information regarding the use of that product to a "learned intermediary" who then assumes that position of interacting with the consumers of that product in their position as medical professionals.

Ordinarily, product manufacturers have a duty to make and sell products that are reasonably safe and not defective; if that is not possible, (as in the case of inherently dangerous products) the duty of manufacturer becomes one of warning about known defects or dangers. Legal theory recognizes that drugs, by their nature are 'inherently dangerous.'

Liability exposure to physicians may be increased when drugs are prescribed 'off-label;' however, the standard to which the practitioner is held is that of 'reasonableness.' Liability can arise from a failure to conform to the standard of care. In an analysis of whether or not an off-label prescription meets the standard of care, the determining factor is the level of scientific or clinical evidence available to support the off-label use; and secondarily. In general, the more scientific evidence there is to support a given off-label use, the more likely it is that the off-label use will be found to conform to the standard of care.

In the case of an adverse event, malpractice claims typically focus on the following types of off-label uses: (a) where the drug is prescribed for an unapproved indication as per the product labeling; (b) instances the dose prescribed deviates significantly from labeling recommendations; and (c) instances where patient is demographically outside (pediatrics, geriatrics) the populations in which the clinical trials supporting the labeling were conducted.

When prescribing a drug for clinical indications outside the scope of FDA approval and labeling, the practitioner will be held to a higher than usual standard to show that a risk-benefit analysis balancing the potential risk to the patient against the potential benefits occurred.

Risk minimization strategies center on careful documentation in the medical record. At the very least, there should be a documentation of the medical reasoning on which the prescription was based. Additional levels of risk minimization might include informed consent and a reference in the medical record to any peer reviewed publications which support the prescribing decision. In the case of off-label prescribing, such supplemental documentation may, in addition to potentially insulating the practitioner from liability in the case of malpractice litigation, may also be necessary in the case of an insurance payer or false claims audit to support 'medical necessity.'

SUGGESTED READING/REFERENCES

Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).

Richardson v. Miller, 44 S.W.3d 1, 13, n.11 (Tenn. Ct. App. 2000).

Szalados JE. "Statutory and Regulatory Controls for Drug Development" in Pharmaceutical Law: Regulation of Research, Development, and Marketing – 2008 Supplement. Clark ME. Ed. BNA Books. Pp 1 – 982. 2008. (ISBN 978-1-57018-765-0).