Package inserts and the standard of care

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A number of pending and new claims involve diet drugs, hormone replacement therapy, cerivastatin (Baycol), oxycodone (OxyContin), troglitazone (Rezulin), thimerosal, and nefazodone hydrochloride (Serzone). One issue is intertwined in all of these claims: the relation between a medication's package insert (also referred to as product information, prescribing information, or *Physicians' Desk Reference* [PDR] listing) and the standard of care applicable to a prescribing physician. In a lawsuit, the manufacturer will attempt to use this information to deflect blame away from it and toward the prescribing physician as part of a general defense strategy or to establish the applicability of the "learned intermediary" doctrine. In addition, juries often attach a great deal of significance to package insert information and can be led to believe that this information sets forth a standard of care or practice guideline. Therefore, package insert information is used by claimants in drug litigation claims and mainstream malpractice cases to establish and/or support opinions about the applicable standard of care and deviations from that standard.

For these reasons, the purpose of package insert information (whether in the form of product information, prescribing information, or PDR entry) and its relation to the practice of medicine needs to be understood and communicated to the court and jury throughout the defense of a claim that centers on the use of a medication. Otherwise, the prescribing physician runs a risk of being unfairly judged on information that is not meant to establish or reflect the applicable standard of care, does not contain or set forth a standard of care, and is not a practice guideline.

PRODUCT INFORMATION

For the purposes of this article, the term "package insert" describes all forms of product information (the insert, prescribing information, and PDR listing). As utilized by the pharmaceutical industry, product information and prescribing information appear to be global terms of reference about a product's characteristics, risks, and recommended uses. The package insert and PDR listing appear to be subsets of this information. The package insert refers specifically to the product information that is included with the medication itself. Sometimes this information is contained only in the bulk form of the medication, from which prescriptions are filled or samples are distributed. On occasion, for example, with oral contraceptives, the insert comes with the medication distributed to the patient by the pharmacy. A PDR listing contains Food and Drug Administration (FDA)–approved product information that is contained in the main PDR volume and its supplements A and B. In the context of pharmaceutical claims, the information most frequently at issue is that contained in the PDR. This is the information that almost all prescribing physicians have access to through their receipt of complimentary copies of the PDR.

Keep in mind that a medication's manufacturer composes information such as the package insert as part of the FDA's regulatory scheme. This information is not created to establish a medical standard of care but rather is required for a manufacturer to market, advertise, and promote a medication (1). The purpose is to inform the consumer of the risks of taking the medication, which theoretically limits the manufacturer's exposure to tort liability for a medication (2). Understanding this background is the first step to effectively dealing with this information.

THE PDR

The PDR is a compendium of information on prescription medications that is published annually with 2 supplements by Thomson Medical Economics. The medication's manufacturer provides the information that is contained in the PDR and pays for its publication. Thomson Medical Economics does not independently verify or investigate the representations and recommendations that are part of each medication's listing; instead, it checks only for grammar and spelling (3).

The main hardbound volume of the PDR is distributed in November or December of the preceding year. For example, the main hardbound 2004 PDR will be sent to physicians in November or December 2003. Supplement A is sent out in June, and supplement B is sent out in mid September. The deadline for submission of information to Thomson Medical Economics for inclusion in the main volume is September of the preceding year (3). Thus, manufacturers must submit information by September 2003 to be included in the main 2004 volume. To be included in supplement A, information must be submitted by April, and to be included in supplement B, information must be submitted by July (3).

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ROLE OF THE PRODUCT INFORMATION IN PATIENT TREATMENT

FDA position

In the context of health care liability claims, the key question is the role, if any, of the package insert in the evaluation of physician conduct. Primarily, this question arises when a prescribing physician utilizes a medication for an indication or at a dosage that is not addressed in or recommended by the package insert (4). By law, however, the FDA cannot regulate the use of a medication by a prescribing physician, and the Federal Food, Drug, and Cosmetic (FD&C) Act (the legislation behind the package insert requirements) does not limit the manner in which a physician may prescribe an FDA-approved medication. The FDA recognizes that once a medication is approved for marketing, a physician may prescribe that medication for indications that are not listed in the package insert (5). These uses are referred to as unapproved, unlabeled, or off-label uses. In addition, the FDA recognizes that there are situations in which the "appropriate and rational" use of a medication may not be reflected by the package insert and may, instead, be reflected by experience and reports in the medical literature (5). More importantly, the FDA's position is that "with respect to its role in medical practice, the package insert is informational only" (5). Thus, the FDA does not take the position that the package insert establishes the medical standard of care.

The medical profession's position

Prescribing physicians have also addressed this issue in medical publications, most commonly in the context of the use of medications in pediatric patients before the Food and Drug Administration Modernization Act of 1997 (FDAMA). Before 1997, very few medications had specific indications for use in pediatric patients because manufacturers did not generally study medications in this patient population. The FDAMA requested drug manufacturers to conduct pediatric studies for new drugs and drugs already on the market in exchange for an additional 6 months of market exclusivity because pediatric patients were often prescribed medications without the benefit of studies to document the safety and efficacy of medications in them or without studies to establish age-appropriate doses of the medication (6).

In this context, before the FDAMA, well-respected physicians recognized and supported the notion that the prescription of medications for off-label uses was entirely proper (4, 7). The caveat was, however, that such use had to be "based on reasonable medical evidence, done in good faith in the best interests of the patient, and done without fraudulent intent," with the "same judgment and prudence . . . exercised in medical practice in general" (8). Physicians also recognized that if a physician denied a patient a potentially beneficial treatment solely because such use was not approved in the package insert, the physician could be subject to a claim for medical malpractice (8). These positions show that the medical profession recognizes that the package insert does not establish the standard of care.

American Medical Association position

The American Medical Association (AMA) has also addressed this situation in its House of Delegates policies. With respect to the PDR generally, the AMA states that a medication package insert "should not be regarded as a legal standard of acceptable or accepted medical practice nor as a substitute for clinical judgment or experience nor as a limitation on usage of the drug in medical practice" (9). The AMA further states that although the PDR is one of many resources for a physician, it "does not establish the sole standard of appropriate use of drugs in the practice of medicine" (10). Lastly, the AMA's position is that "it is appropriate and legal for physicians to prescribe approved drugs for uses not included in their official labeling when they can be supported as rational and accepted medical practice" (11). Clearly, the AMA does not believe the package insert establishes the standard of care.

PDR position

Thomson Medical Economics, the publisher of the PDR, similarly supports the FDA, physician, and AMA positions. In the foreword to each PDR is a disclaimer that states:

> The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling (12).

Pharmaceutical industry position

While representatives of the pharmaceutical industry will tout the completeness and validity of the information in their product's package inserts, in deposition they generally agree the product insert is a legal, not a medical, document. Further, they agree that the product insert does not reflect and is not meant to represent or reflect a summary or synopsis of the medical standard of care on the use of the medication. In fact, such representatives have admitted, and it is well known, that companies will provide, upon a request from a physician, literature that addresses off-label uses of their medications.

THE LEGAL EFFECT OF PRODUCT INFORMATION IN DETERMINATION OF THE STANDARD OF CARE

Regardless of this uniform agreement and recognition that product inserts do not define the standard of care for the use of prescription medications, in a health care liability claim, the key concern is how courts will rule on this issue. The rulings are not uniform, can vary drastically from state to state, and are largely dependent on the evidence before the court in the form of expert witness testimony on this issue.

In terms of the ultimate legal effect of package insert information in malpractice claims, there are 2 questions. First, does this information establish the applicable standard of care, or can it be used as evidence in the determination of the applicable standard of care? Second, can this information be used, like any other "learned treatise" (13), in the cross-examination or impeachment of a witness? Generally, the package insert does not, in and of itself, establish the standard of care. It can be, and frequently is, used to support or cross-examine an expert on the standard of care.

Generally, courts have ruled that the package insert is not *prima facie* (14) evidence of the applicable standard of care (1). Illinois and Minnesota courts, however, have taken the position

that the package insert is *prima facie* evidence of the standard of care (15). In Minnesota, this is referred to as the *Mulder* rule. The Minnesota Supreme Court, in enunciating the *Mulder* rule, stated:

> Where a manufacturer recommends to the medical profession 1) the conditions under which its drug should be prescribed; 2) the disorders it is designed to relieve; 3) the precautionary measures which should be observed; and 4) warns of the dangers which are inherent in its use, a doctor's deviation from such recommendations is prima facie evidence of negligence if there is competent medical testimony that his patient's injury or death resulted from the doctor's failure to adhere to the recommendations (16).

The *Mulder* rule was subsequently modified by the Minnesota Supreme Court to state that for a package insert to be *prima facie* evidence of the standard of care, the package insert's recommendations and instructions must be "clear and unambiguous" (17).

The *Mulder* rule, however, does not appear to be the position of the courts in Texas and most other states. In Texas, package insert information can be considered evidence of the standard of care only if it is established as such by expert medical testimony or if it is shown to be a "learned treatise" (13) by expert testimony (18). If there is no expert testimony that establishes the package insert information as the standard of care or a learned treatise, it is proper for the court to exclude that information from evidence (18). If the medical experts agree that the package insert is relied on by physicians, use of the package insert as a learned treatise is appropriate (19). This appears to be the position followed by most states on this issue (1, 2, 20).

This evaluation shows that prescribing physicians need to be careful about situations in which they utilize medications for indications and at dosages outside of what is described in the package insert. In those situations, although the FDA, physicians, the AMA, the publisher of the PDR, and the pharmaceutical industry all generally recognize that the package insert does not establish the standard of care, a trial or appellate court may find otherwise. For the package insert to be considered in evaluation of the applicable standard of care in a malpractice case, it appears that the only requirement is that an expert testifies that it reflects the standard of care or qualifies as a learned treatise. This is not a difficult burden, and one should expect that a malpractice claimant can and will obtain such testimony. To respond, the defense needs to utilize the FDA, physician, AMA, and PDR positions described above, as well as have specific medical references or practice guidelines available that support as reasonable and rational any uses of a medication that are not reflected in the package insert. Otherwise, there is a real and significant risk of finding the physician's conduct difficult to justify and defend in court.

1. See *Morlino v. Medical Center of Ocean County,* 706 A.2d 721 (N.J. 1998).
2. *Spensieri v. Lasky,* 723 N.E.2d 544 (N.Y. 1999).
3. See Oral and Videotape Deposition of Dikran Barsamian, in the matter of *Rezulin Products Liability Litigation,* MDL-1348, August 16, 2001. (Mr. Barsamian was the national sales manager for Medical Economics in 1998 when Rezulin was on the market in the USA. At the time of his deposition in 2001, he was vice president of sales and marketing for the Directory Services Group of Medical Economics.)
4. Blumer JL. Off-label uses of drugs in children. *Pediatrics* 1999;104(3 Pt 2): 598–602.
5. *FDA Drug Bulletin* 1982 (April);12(1):4–5.
6. American Academy of Pediatrics. Press statement on the safety of medicines for children, January 11, 2001.
7. American Academy of Pediatrics. Testimony by the American Academy of Pediatrics before the Subcommittee on Human Resources and Intergovernmental Relations Government Reform and Oversight Committee, US House of Representatives, "Off-label drug use and FDA review of supplemental drug applications," September 12, 1996.
8. American Academy of Pediatrics Committee on Drugs. Unapproved uses of approved drugs: the physician, the package insert, and the Food and Drug Administration. *Pediatrics* 1996;98:143–145.
9. American Medical Association, House of Delegates Policy H-115.994, *Physicians' Desk Reference*.
10. American Medical Association, House of Delegates Policy H-120.993, *Physicians' Desk Reference*.
11. American Medical Association, House of Delegates Policy H-120.992, Prescription of Drugs.
12. Foreword to the fifty-seventh edition. In *Physicians' Desk Reference,* 57th ed. Montvale, NJ: Thomson Medical Economics, 2003.
13. Rule 803 (18), *Texas Rules of Evidence* (West 2002). ("To the extent called to the attention of an expert witness upon cross-examination or relied upon by the expert in direct examination, statements contained in published treatises, periodicals, or pamphlets on a subject of history, medicine, or any other science or art established as a reliable authority by the testimony or admission of the witness or by other expert testimony or by judicial notice" is an exception to the hearsay rule. "If admitted, the statements may be read into evidence but may not be received as exhibits.")
14. *Black's Law Dictionary,* 6th ed. West, 1991. *(Prima facie* evidence is defined as "evidence good and sufficient on its face." It can also be defined as "that quantum of evidence that suffices for proof of a particular fact until the fact is contradicted by other evidence.")
15. *Ohligschlager v. Proctor Community Hosp.,* 303 N.E.2d 392 (Ill. 1973); *Mulder v. Parke Davis & Co.,* 181 N.W.2d 882 (Minn. 1970).
16. *Mulder,* 181 N.E.2d at 887.
17. *Lhotka v. Larson,* 238 N.W.2d 870 (Minn. 1976).
18. See *Kinzer v. Landon,* WL 354880 (Tex. App.—Houston [14th Dist.] 1996) (unpublished opinion); *Reynolds v. Warthan,* 896 S.W.2d 823 (Tex. App.—Tyler 1995, no writ); *Davis v. Marshall,* 603 S.W.2d 359 (Tex. App.—Houston [14th Dist.] 1980, writ ref'd n.r.e.).
19. See *Kahanek v. Rogers,* 12 S.W.3d 501 (Tex. App.—San Antonio 1999, writ denied).
20. See *Craft v. Peebles,* 893 P.2d 138 (Hawaii 1995); *Ramon v. Farr,* 770 P.2d 131 (Utah 1989).