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Issues and Trends in Drug Product Labeling

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Introduction

Manufacturers of prescription medications will soon be subject to increased Food and Drug Administration (FDA) oversight with respect to their product labels. The FDA, acting under the authority granted in Section 505(o)(4) of the federal Food, Drug, and Cosmetic Act (FDCA), has recently issued a draft guidance document outlining its intent to exercise its power to unilaterally change a drug's (or a class of drugs') labeling based upon the FDA's review of new safety data. The process proposed by the FDA is remarkably swift, and it affords manufacturers relatively little time to respond to labeling changes requested by the FDA.

Despite the FDA's increased power and control over product labels, it is unlikely that increased governmental control will have any effect on the preemption issue as it relates to state failure-to-warn claims. The US Supreme Court, in its second ruling on the preemption issue in as many years, recently clarified that only failure-to-warn claims against generic manufacturers are preempted—claims against manufacturers of branded drugs are not. Notably, because a branded manufacturer is still subject to the "changes being effected" (CBE) requirements under 21 C.F.R. §§ 314.70 and 601.12, and therefore obligated to institute certain safety-related labeling changes when warranted, future preemption challenges to state failure-to-warn claims against branded manufacturers will likely be unsuccessful.

Additionally, manufacturers face increased exposure under state failure-to-warn claims as both Congress and the courts chip away at the learned intermediary defense. The US House of Representatives recently introduced the Consumer Protection Act of 2011, which would eliminate the learned intermediary defense in all product liability suits. In the absence of federal law, many courts are trending towards finding broader exceptions to the learned intermediary defense, including one recent Texas appellate court that found that "patient care materials," arguably intended to assist patients undergoing treatment, constituted "direct-to-consumer" advertising, thereby negating the manufacturer's learned intermediary defense.

The following provides manufacturers with insight on the FDA's new and greatly expanded powers to unilaterally order labeling changes, and advice for avoiding civil exposure from state failure-to-warn claims.

Understanding Section 505(o)(4) and the New FDA Procedures for Safety Labeling

Section 505(o)(4) of the FDCA (21 U.S.C. § 355(o)(4)), added by Section 901 of the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), significantly increases the FDA's power to unilaterally require drug and biological product application holders to make safety-related labeling changes based upon post-approval safety data. Specifically, Section 505(o)(4) authorizes the FDA to require safety labeling changes for:

1. Prescription drugs with an approved new drug application (NDA)
2. Biological drugs with an approved biologics license application (BLA)
3. Prescription drug products with an approved abbreviated new drug application (ANDA) if the NDA reference-listed drug (RLD) is not currently marketed

Section 505(o)(4) does not apply to non-prescription (over-the-counter) drugs approved under an NDA.

Although the FDAAA was passed in 2007, the FDA just recently issued draft guidance setting forth its planned implementation of its new powers. Draft Guidance, April 2011, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf. While the draft guidance is not yet binding, it evidences the FDA's intent to proactively order safety labeling changes, marking a drastic change from its past practice of relying upon manufacturers to make post-market changes. The draft guidance, if implemented in its current form, sets forth the FDA's new and expansive power to unilaterally request and *order* labeling changes with respect to individual drugs as well as entire classes of drugs.

It is important to note that the FDA has indicated that not all labeling changes related to safety will be required and reviewed under Section 505(o)(4) of the FDCA. Rather, under the FDA's proposed rules, only

safety information that would alter or change the language contained in the following sections of the label would fall under Section 505(o)(4):

- Boxed warnings
- Contraindications
- Warnings and precautions
- Drug interactions
- Adverse reactions (if the resultant changes are also included in one of the other included sections of the label)

See April 2011 Guidance Document. Notably, the FDA has expressly stated that information that results in changes made *only* to the adverse reactions section of the label, but does not trigger changes to other sections of the label, would not generally trigger the required safety labeling changes under Section 505(0)(4). Additionally, the FDA does not intend to require safety labeling changes under Section 505(o)(4) for minor editorial changes to any part of the labeling. However, new safety information about serious risks that affect a class of drugs will trigger mandatory labeling changes in all drugs within the class under the authority of Section 505(o)(4).

Additionally, the FDA will likely require changes to existing medication guides or the creation of medication guides if changes to the labeling are required under Section 505(o)(4).

The application holder should continue to supplement labeling changes using the standard procedures set forth in 21 C.F.R. §§ 314.70 and 601.12 for those labeling changes that fall outside the scope of Section 505(o)(4). As discussed in greater detail below, manufacturers should adopt proactive policies and procedures as part of their overall FDA compliance program, outlining a process for promptly and effectively responding to any FDA notification letters. A responsive team should also be identified in advance, and the manufacturer should immediately notify their regulatory counsel.

Past Practices

Prior to the passing of Section 505(o)(4) of the FDCA, the FDA could request that manufacturers make post-approval labeling changes to address serious risks, but could not unilaterally require labeling changes. If an application holder disagreed with or ignored the FDA's requested labeling changes, the FDA was left with few options short of withdrawing approval of the drug or initiating an enforcement action against the approval holder for marketing a misbranded drug. The FDA has historically been hesitant to initiate proceedings to withdraw its approval of drugs over labeling changes—particularly in cases where the drugs are still benefitting patients despite the risks—and has instead encouraged "voluntary withdrawals" only in situations where post-marketing surveillance evidenced that the risks of the product outweighed the benefits (e.g., Meridia, Pergolide, Pondimin, Redux). For example, American Home Products Corp. withdrew its diet medications Pondimin (fenfluramine) and Redux (dexfenfluramine) only after the FDA, armed with dozens of case reports of unexpected claims of heart valve regurgitation, "requested" the withdrawal. The FDA, alarmed by reports from researchers at the Mayo Clinic and Mayo Foundation of rare valvular disease in women taking the medications, alerted medical doctors of the reports and requested that health care professionals report any such cases to the FDA. After receiving sixty-six additional reports of heart valve disease, the FDA first suggested the manufacturer strengthen the warnings. However, as the reports of valvular regurgitation increased, the FDA very vocally and publicly requested the manufacturer withdraw the two medications from the market. *See FDA Announces Withdrawal Fenfluramine and Dexfenfluramine (Fen-Phen)*, www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm179871.htm.

Similarly, the FDA typically focuses its misbranding enforcement efforts against manufacturers making unapproved efficacy or therapeutic benefit claims (e.g., dietary supplements, injectable cellulite, and fat removal treatments).

Application holders typically responded to the FDA's request for labeling changes by negotiating appropriate language with the FDA and then submitting a supplement or amended supplement to obtain approval of the changes. Because the FDA could not *require* the requested change, the

approval holder had considerable leverage with respect to the negotiated language. The process was often time-consuming, and the resultant labeling changes did not always adequately address the new risks.

The FDA's Proposed Implementation of Section 505(o)(4) in Future Practices

Under Section 505(o)(4), the FDA can order labeling changes relating to new safety information. "New safety information" is broadly defined in the FDCA as "information derived from a clinical trial, an adverse event report, a post-approval study (including a study under Section 505(o)(3)), peer-reviewed biomedical literature, data derived from the post-market risk identification and analysis system under Section 505(k), or other scientific data deemed appropriate by [the FDA]" about:

- "A serious risk or an unexpected serious risk associated with the use of the drug that [the FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy ("REMS") was required, or since the last assessment of the approved [REMS] for the drug," or
- "The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS]."

21 U.S.C. § 355-1(b) (2010). The FDA has indicated in its draft guidance that it may rely upon a myriad of sources of new safety information, ranging from adverse event reporting to communications with foreign regulatory authorities. New safety information may be derived by the FDA through various means, including:

- New analysis of existing information
- Assessment of the risks and benefits of the drug as it pertains to a new use of the drug, a new indication for the drug, or the use of the drug in a new population
- Information on the effectiveness of a previously approved REMS obtained since the last assessment of that REMS

Id. Once the FDA has learned of new safety information, it plans to convene a multidisciplinary team to evaluate the data and the drug's label. Where a class of drugs might be implicated by the new safety information, the FDA anticipates that it will first work to identify all drugs within the class that may be affected. The FDA then plans to involve all review divisions involved with the various drugs, as well as the Office of Generic Drugs, the Unapproved Drugs Coordinator, and the Office of Compliance where appropriate.

The FDA's Proposed Procedures for Effectuating Section 505(o)(4) Labeling Changes

FDA Notification Letters

If the FDA determines that new safety information about a drug should be included in its labeling, the FDA plans to send a notification letter to the application holder, which will outline:

- The source of the new safety information
- A brief description of the subject of the new safety information (i.e., a serious or unexpected serious risk associated with the drug or the effectiveness of the REMS)
- The FDA's proposed labeling changes
- Instructions to the application holder about whether to submit a "prior approval supplement" (FDA approval required) or a "CBE supplement (no FDA prior approval required)

Application Holder Response

Under the FDA's draft guidance document, after receiving a notification letter from the FDA, the application holder must respond to the FDA within thirty days of the date the notification letter is issued in one of two ways:

1. Submit a supplement with the proposed labeling changes reflecting the new safety information or that contains proposed edits or counterproposals to the language requested by the FDA

2. Submit a rebuttal statement notifying the FDA of the reasons why the FDA's proposed labeling changes are not warranted.

The application holder should submit a CBE supplement if the application holder agrees to the FDA's proposed language as is and if the notification letter applies to only one application (as opposed to a class of drugs). The application holder should submit a "prior approval supplement" in all other situations where the application holder concedes that a labeling change is warranted but disagrees as to the language proposed by the FDA.

NDA and BLA holders must bear in mind that if they become aware of new safety information, they are still obligated under 21 C.F.R. 314.70 and 601.12 to proactively submit the labeling changes to the FDA, regardless of the new processes established by Section 505(o)(4).

Failure to respond to a notification letter will result in forfeiture by the application holder of any review or discussion by the FDA. The FDA has indicated that it may then issue an order directing the labeling change.

FDA Review of the Application Holder's Supplement or Rebuttal Statement

Section 505(o)(4)(C) of the FDCA provides only that the FDA must "promptly review and act upon" the application holder's supplement or rebuttal statement, but does not specify a timeframe under which the FDA must act. The FDA's draft guidance provides the FDA's two proposed timelines to implement Section 505(o)(4)(C)'s "promptly review and act upon" mandate.

Labeling Supplements

In situations where the application holder agrees that changes to the label should be made as set forth in the FDA's notification letter, the FDA has indicated that its "goal" is to approve the labeling within thirty calendar days of the application holder's supplement. Similarly, where the application holder agrees that changes should be made, but disagrees with the language proposed by the FDA, if the application holder's alternate proposed language is acceptable to the FDA and can be approved without changes,

the FDA intends to approve the language within thirty calendar days of receipt of the same.

However, where the application holder's alternate language cannot be approved by the FDA without changes, the FDA intends to initiate a discussion period to discuss the proposed revisions, which will begin on the date the FDA receives the application holder's proposed language and last no more than thirty days (unless an extension is warranted). The FDA has not articulated under what basis extensions will be given, but it is safe to assume that extensions are more likely to be given for drugs deemed necessary or highly beneficial to higher-risk patient populations, or in situations where the clinical data is still being evaluated by the medical community. The FDA will make a final decision on the labeling changes within fifteen days of the conclusion of the discussion period. If the FDA and the application holder reach a consensus on the revised labeling, the FDA will send the application holder a supplement approval letter. If, however, no consensus is reached, Section 505(o)(4)(E) authorizes the FDA to order the application holder to make the FDA's requested labeling changes.

Rebuttal Statements

If the application holder disagrees with the FDA that labeling changes are warranted, the FDA will conduct a preliminary review of the application holder's rebuttal statement. The guidance document indicates that the FDA will notify the application holder if it accepts the application holder's rationale as to why labeling changes are not warranted, but it does not set forth a timeframe for the FDA to notify the application holder. If the FDA rejects the application holder's reasons why labeling changes are not warranted, the FDA will commence a thirty-day discussion period with the application holder. The FDA has indicated that within fifteen days of the completion of the discussion, it will either notify the application holder if a consensus has been reached or order its version of the labeling changes under the authority of Section 505(o)(4)(E).

Given the tight timeline proposed by the FDA, it is important for manufacturers to proactively put in place procedures for responding to FDA notification letters. In-house compliance officers, medical directors,

product managers, and regulatory counsel should be included on the response team.

FDA Labeling Change Orders

If no consensus is reached by the application holder and the FDA, or if the application holder fails to respond to a notification letter, the FDA is authorized by Section 505(o)(4)(E) to unilaterally order changes to the product labeling. The FDA has indicated that it anticipates that labeling change orders will be "rare." The labeling change order will require the application holder to submit a CBE supplement within fifteen calendar days of the date of the order for specified changes to the labeling. The FDA intends to set forth in its order the specific wording of the labeling changes.

The application holder must then either submit a CBE supplement using the language mandated by the labeling change order or appeal the labeling change order within five calendar days. Should the application holder fail to submit a supplement or file an appeal, it will be in violation of the FDCA.

The FDA anticipates that it will approve all CBE supplements within fifteen days of receipt from the application holder. The application holder will then be expected to publish the new labeling on its website within ten calendar days. The FDA has not yet set forth timeframes for amending package inserts, patient package inserts, and medication guides, but it intends to issue guidance on this topic in the future. Absent concrete deadlines from the FDA, manufacturers should be prepared to amend all packaging and materials related to the drug as soon as possible. Sales staff should be trained on any changes and, where applicable, press releases circulated. All changes should be made in coordination with the manufacturer's compliance officers and regulatory counsel.

<u>What This Means to Application Holders</u>

Application holders are still obligated under 21 C.F.R. §§ 314.70 and 601.12 to self-monitor the safety and effectiveness of their products and provide to the FDA revised proposed labeling including warnings about any newly discovered "clinically significant hazard as soon as there is reasonable evidence of a causal association with the drug." *See also* 21 C.F.R. §

201.57(c)(6) (2006). While ANDA holders cannot make labeling changes through the same process as branded drugs, ANDA holders should be mindful of their continuing duty to inform the FDA of certain adverse events and to include safety information in their annual reports. *See* 21 C.F.R. § 314.80 *et seq*.

Section 505(o)(4) essentially gives the FDA power to unilaterally amend the labeling of an approved drug or biologic (or an entire class of drugs or biologics) when the FDA becomes aware of new safety information. Under the FDA's draft guidance, it appears the FDA intends to wield its new powers to the fullest extent authorized by the statute. Labeling changes could very often be ordered within seventy-five days of the FDA first serving the application holder with a notification letter. An application holder will likely have only thirty days to respond to a notification letter, and the anticipated "discussion period" to negotiate the labeling changes with the FDA could be as short as thirty days. The FDA has provided no guidance as to the specifics of the actual negotiation process or what additional data or information it will consider.

It is therefore crucial for manufacturers to track safety trends and data affecting not only their product, but also drugs within the class of their product, to anticipate any potential labeling change requests by the FDA. Manufacturers must be prepared to act quickly should they receive a notification letter, and have the data compiled to refute any suggested changes made by the FDA. There may be situations where it is advantageous (or legally required under 21 C.F.R. § 314.70) for the manufacturer to proactively initiate the labeling change through the CBE process rather than waiting for the FDA to act.

The FDA has broad authority to enforce Section 505(o)(4) under Section 902 of the FDAAA. Failure to comply with the FDA's labeling change order could result in:

- Unapproved new drug charges under Section 505(o)(1) of the act
- Drug misbranding charges under Section 502(z) of the act
- Civil monetary penalties under Section 303(f)(4) of the act of up to $250,000 per violation ($1 million maximum per violation

adjudicated in a single proceeding), which doubles every thirty days the application holder fails to remedy the labeling "violation" up to $1 million per period and $10 million for all violations adjudicated in a single proceeding

- Seizure of the product and injunctive relief (for example, the FDA recently seized $6 million worth of products from Tirad Group for failing to comply with the FDA's good manufacturing practices regulations. *See* Press Release, FDA, *Federal Government Takes Action Against Drug Manufacturer and Distributor* (June 13, 2011), *available at* www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258864.htm.

Preemption and Failure-to-Warn Claims: Branded versus Generic

The Supreme Court has addressed the issue of whether federal law preempts state law claims of inadequate warnings in prescription pharmaceuticals twice in the past two years. In 2009, the Supreme Court decided the landmark case of *Wyeth v. Levine*, holding that in terms of branded drugs, federal law does not preempt state law tort claims. In 2011, in *Pliva Inc. et al v. Mensing*, the Supreme Court decided that in terms of generic drugs, federal law does preempt state law tort claims. Although the cases are factually quite similar, the Supreme Court reached opposite results, leaving it to Congress to resolve this seeming conflict in the laws governing branded versus generic pharmaceuticals.

Branded Drugs: Wyeth v. Levine

In *Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187 (2009), the US Supreme Court held that federal law does not preempt state law failure-to-warn claims against brand-name drugs, quelling a trend of case law supporting the FDA's and industry's arguments in support of preemption. Levine claimed that Wyeth, the manufacturer of the prescription medication Phenergan, failed to provide an adequate warning about the risks of administering *Phenergan* via IV push, resulting in severe injuries to the plaintiff. Wyeth's arguments that Levine's claims were preempted by federal law because the FDA had approved Phenergan's labeling were rejected by both the trial court as well as the Vermont Supreme Court. The Supreme Court agreed with Vermont, finding that FDA labeling approval does not

provide pharmaceutical manufacturers with a complete defense to state failure-to-warn tort claims. *Id.* at 1191.

Levine seemed, to many in the industry and the FDA, to present the ideal factual case for the Supreme Court to find in favor of preemption, largely because of the amount of communication between Wyeth and the FDA over the years about Phenergan's labeling. *Phenergan* was first approved in 1955. *Id.* at 1192. Wyeth submitted supplemental new drug applications in 1973 and 1976, which were approved after the FDA suggested more labeling changes. *Id.* Wyeth submitted a third supplemental application in 1981 after a new FDA rule regarding drug labels. *Id.* In 1987, the FDA suggested different warnings about the risks of arterial exposure. *Id.* In 1988, Wyeth submitted changes made pursuant to those proposed changes. *Id.* In 1996, the FDA requested to see Wyeth's current label and instructed Wyeth to retain the language in that label regarding injecting the drug into the artery. *Id.* Finally, in 1998, the FDA approved the 1981 application and instructed Wyeth that the final printed label had to be identical to the approved package insert. *Id.*

Despite Wyeth's continued compliance with the FDA's numerous requirements over the years, the trial court instructed the jury that compliance alone did not establish that the warning was adequate because FDA regulations "permit a drug manufacturer to change a product label to add or strengthen a warning about its product without prior FDA approval so long as it later submits the revised warning for review and approval." *Id.* at 1193. The Vermont Supreme Court affirmed, holding that Wyeth "could have warned against [the risk] without prior FDA approval, and because, federal labeling requirements create a floor, not a ceiling, for state regulation." *Id.* The Supreme Court, recognizing the surge of conflicting case law regarding preemption, acted. *Id.*

Wyeth argued for preemption on two grounds: (1) that it would have been impossible for it to comply with the state law duty to modify Phenergan's labeling without violating federal law, and (2) that recognition of Levine's state tort action creates an unacceptable obstacle to congressional intent because it substitutes a jury's decision for the expert judgment of the FDA. *Id.* at 1194.

At the core of the Supreme Court's decision were the CBE regulatory provisions governing branded drug manufacturers. Although the FDA approves the exact text of proposed drug labels and generally prohibits manufacturers from making changes to already approved labels without submitting supplemental applications, manufacturers are permitted to amend labels prior to FDA approval in very limited circumstances. *Id.* at 1196, *citing* 21 CFR § 314.70(c)(6)(iii)(A)(C). Pursuant to 21 C.F.R. § 314.70(c)(6)(iii)(A)(C), manufacturers are permitted to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product" before getting FDA approval. *Id.* As long as the manufacturer submits a supplemental application at the time of the label change, the manufacturer need not wait for FDA approval. *Id.* Levine argued that because Wyeth was aware of at least twenty similar incidents prior to the injury at issue, Wyeth could have reviewed the data and added a stronger warning to the label under the CBE process. *Id.* 1197.

Wyeth first countered that it would have been impossible for Wyeth to comply with the state law duty to modify the drug's label without violating federal law, noting that the FDA bears the primary responsibility for drug labeling. *Id.* at 1198. The court disagreed, finding that "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* Therefore, the court found that when Wyeth learned of the risk at issue, Wyeth "had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval." *Id.* Accordingly, the court found that it was not impossible for Wyeth to comply with both federal and state law. *Id.* at 1199. "The CBE regulation permitted Wyeth to unilaterally strengthen its warnings, and the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change." *Id.*

The court also rejected Wyeth's second argument that Levine's state law claim created an unacceptable obstacle to the execution of Congress's full purposes and objectives because it, in effect, substituted a jury's decision

about drug labeling for the expert judgment of the FDA. Wyeth reasoned that such tort claims are preempted because they "interfere with Congress's purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives." *Id.* The court rejected this argument, noting that if Congress thought that state lawsuits posed an obstacle to its objectives, it would have enacted a preemption provision. *Id.* at 1200. The court similarly rejected the FDA's position, set forth in the preamble to a 2006 FDA regulation, that FDA approval of labeling preempts conflicting or contrary state law. *Id.* The court recognized that agencies have a unique understanding of the statutes they administer, but noted that they lack the authority to decide preemption issues. *Id.* at 1201.

The court, setting out the public policy supporting its opinion, reasoned that the FDA casts "federal labeling standards as a floor upon which states could build." *Id.* at 1202. The court noted that the FDA "has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge." *Id.* The court further reasoned that because state tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly, such suits serve a distinct compensatory function that may motivate injured persons to come forward with information. *Id.*

The Supreme Court, seemingly closing the door on the preemption argument, concluded that "Wyeth has not persuaded us that failure-to-warn claims like Levine's obstruct the federal regulation of drug labeling. Congress has repeatedly declined to preempt state law." *Id.*

Generic Drugs: PLIVA Inc. et al v. Mensing

In *PLIVA Inc. et al v. Mensing*, 131 S. Ct. 2567 (U.S. 2011), a case nearly identical to *Wyeth* in all aspects but for the fact that the drug at issue was generic, the Supreme Court changed course and held that state law failure-to-warn claims are preempted by federal drug regulations.

The drug at issue, metoclopramide, is the generic form of Reglan, which was first approved by the FDA in 1980. *Id.* at 2572. In 1985, the label was

modified to state that tardive dyskinesia could develop, and that use longer than twelve weeks was not recommended. *Id.* In 2009, the FDA required a black box warning, which stated that "treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. Treatment with metoclopramide for longer than twelve weeks should be avoided in all but rare cases." *Id.* at 2573.

Plaintiffs in the underlying actions took the generic form of the drug in 2001 and 2002 after their doctors prescribed Reglan, and both developed tardive dyskinesia after several years of taking the drug. *Id.* Both sued the generic manufacturers alleging state failure-to-warn claims. *Id.*

The manufacturers urged that federal law preempted the state law claims, arguing that federal law required them to use the same label as the brand-name drug. *Id.* Thus, they could not independently alter their label if the brand name did not, making it impossible to comply with the state law and federal law. *Id.* The Fifth and Eighth Circuits disagreed, finding that federal law did not preempt the state law claims. *Id.*

The Supreme Court, outlining the statutory history, distinguished the laws governing branded and generic drugs. Since the 1962 Drug Amendments to the FDCA, manufacturers looking to gain approval to market a new drug have had to prove that the drug was safe and effective and that the label was accurate and adequate. *Id.* at 2574. In 1984, the Drug Price Competition and Patent Term Restoration Act, or Hatch-Waxman Amendments, were passed, which stated that generic drugs can "gain FDA approval simply by showing equivalence to a reference listed drug that has already been approved by the FDA." *Id.* The generic label must be the same as the brand-name label. *Id.* "As a result, brand-name and generic drug manufacturers have different federal drug labeling duties. A brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label. A manufacturer seeking generic drug approval, on the other hand, is responsible for ensuring that its warning label is the same as the brand name's." *Id.*

The court thereby rejected the argument that the generic manufacturers could have changed their labels through the CBE process because the CBE regulation allows "changes to generic drug labels only when a generic drug

manufacturer changes its label to match an updated brand name label or to follow the FDA's instructions." *Id.*

The court also rejected the argument that the generic drug manufacturers could have used "dear doctor" letters to warn prescribing physicians of the dangers. *Id.* at 2576. The court deferred to the FDA's position that dear doctor letters are labeling, and thus any letters must be consistent with the brand-name drug's labeling. *Id.* If a dear doctor letter contained a new warning, it would no longer be consistent with the brand-name drug's label. *Id.*

The Supreme Court, in addressing the seeming inconsistency between *Wyeth* and *Pliva,* reasoned that *Wyeth* was not to the contrary because it is possible for a brand-name manufacturer to comply with both state and federal law. Specifically, the CBE regulation allows only branded manufacturers, not generic manufacturers, to "unilaterally strengthen [a drug's] warning" without prior FDA approval. *Id.* The court acknowledged that from the perspective of the patients in the instant case, "finding preemption here but not in *Wyeth* makes little sense. Had [the patients] taken Reglan, the brand name drug prescribed by their doctors, *Wyeth* would control and their lawsuits would not be preempted. But because pharmacists…substituted generic metoclopramide instead, federal law preempts these lawsuits… We acknowledge the unfortunate hand that federal drug regulation has dealt [the patients], and others similarly situated, but it is not this Court's task to decide whether the statutory scheme established by Congress is unusual or even bizarre." *Id.* at 2581-82.

Despite the practical unfairness of the decision, the court held firm, noting that "different federal statutes and regulations may, as here, lead to different preemption results. We will not distort the Supremacy Clause in order to create similar preemption across a dissimilar statutory scheme. As always, Congress and the FDA retain the authority to change the law and regulations if they so desire." *Id.*

Homeopathic Drugs v. Over-the-Counter Drugs: Delarosa v. Boiron, Inc.

Though not as significant as the aforementioned Supreme Court decisions, it should be mentioned that at least one federal district court addressed the preemption issue as it applies to the rapidly expanding market of

homeopathic drugs. In *Delarosa v. Boiron, Inc.*, 2011 WL 3102468 (C.D. Cal. July 25, 2011), the plaintiff claimed that defendant Boiron Inc. defrauded consumers with its "Children's Coldcalm" product, a natural or "homeopathic" drug, containing ingredients such as flowers, vegetables, insects, metals, and poison. *Id.* at 1. Children's Coldcalm claimed to provide relief from sneezing, runny rose, nasal congestion, sinus pain, headaches, and sore throat. *Id.* The plaintiff purchased Children's Coldcalm and claimed that the product did not provide the benefits it claimed. *Id.* The defendant moved for a judgment on the pleadings, which the court ultimately denied.

The FDCA, 21 U.S.C. § 301 *et seq.*, "defines 'drug' to include articles, like Coldcalm, that are recognized in the official Homeopathic Pharmacopeia of the United States and includes both prescription and over-the-counter (OTC) drugs." *Id.* at 2. "The FDA evaluates whether non-homeopathic OTC drugs are safe, effective, and not misbranded." *Id.* However, the FDA does *not* evaluate homeopathic OTC drugs, including drugs like Children's Coldcalm. *Id.* at 3. "The Court is unaware of what standards, if any, exist to ensure that homeopathic OTC drugs are safe and effective. The FDA does not impose additional standards for strength, purity, quality, safety, or efficacy on homeopathic OTC remedies. *Id.* at 4.

After a detailed analysis, the court concluded that homeopathic drugs are not preempted by the express preemption clause pertaining to OTC medications. *Id.* at 8. In addition, the court found that even if Children's Coldcalm is not excepted from the express preemption clause, the plaintiff's claims were not preempted. *Id.* at 10. The court found that "Plaintiff's claims, if proven to be true, would simply require Defendant to truthfully state its efficacy or not sell its products; such relief would not impose a state requirement that is 'different from or in addition to, or that is otherwise not identical with' that of the FDCA." *Id.* at 10. The court also rejected an argument for implied preemption. *Id.* at 11. The defendant also argued that the court should refrain from hearing this action because the FDA has "primary jurisdiction." *Id.* The court found that the FDA has "largely abdicated any role it might have had in creating standards for homeopathic OTC drugs." *Id.* Therefore, the court denied the defendant's motion for a judgment on the pleadings. *Id.* at 13.

Interpreting the Rulings Regarding Preemption

It is clear from the *Wyeth* and *Pliva* decisions that the Supreme Court based its decision on the availability of the CBE mechanism to only branded manufacturers. As such, it will fall to Congress to remedy the statutory incongruity between branded and generic drugs, which seems unlikely under the current administration. It seems impossible for Congress to create a mechanism for claimants to bring state law failure-to-warn claims against generic manufacturers without completely subverting the intended goals of the Hatch-Waxman Amendments—namely, to push generic drugs onto the markets. To subject generic manufacturers to the same CBE requirements applicable to branded manufacturers would, in effect, subject them to much of the NDA processes, thereby greatly limiting the ability for generic manufacturers to introduce their products into the market. The FDA's current position that state law failure-to-warn claims should be preempted against both generic and branded manufacturers will not likely be adopted by Congress any time in the near future.

The FDA's expanded power to control changes to drug labeling under Section 505(o)(4) may have little effect on the preemption issue, as branded manufacturers are still subject to the CBE provisions. However, interesting preemption arguments will arise in situations where the claims relate to risks addressed by (and possibly rejected by) the FDA as part of labeling changes initiated by the FDA under Section 505(o)(4).

It should also be noted that, based upon the well-reasoned analysis of the *Delarosa* court, failure-to-warn claims brought against homeopathic OTC drugs are not preempted, as they are largely unregulated by the FDA.

Manufacturers and their counsel need to make intelligent decisions as to when and through what means preemption challenges are made. "Form" preemption affirmative defenses should be avoided and instead evaluated based upon whether the product at issue is a branded versus generic drug (or homeopathic versus OTC drug).

The State of the "Learned Intermediary Defense": Federal and State Trends

Overview of the Learned Intermediary Defense

The learned intermediary defense is often cited as an additional limitation to the liability of drug manufacturers over and above those limitations provided in the federal statutes and preemption doctrine. This state law-based doctrine provides that a manufacturer of prescription drugs or products discharges its duty to warn by providing the physician, or other health care provider, with information about risks associated with those products. The physician then acts as a learned intermediary between the manufacturer and the patient, and any warning given to the physician is deemed a warning to the patient. The learned intermediary doctrine also provides that the failure to provide adequate warning of the risks associated with a prescription product is not the proximate cause of a patient's injury if the prescribing physician had independent knowledge of that risk. Thus, at its core, this defense impacts a finding of proximate cause for a patient's injury based on the warnings provided to or known by the learned intermediary.

The majority of states, currently forty-eight, apply some form of the doctrine even if in limited form. However, several states have questioned its application or the scope of its protection. For example, several states have addressed the application of this defense when a pharmacy is involved and whether a duty to warn extends to that pharmacy. In addition several states, such as Texas, Connecticut, and Montana, have recently issued opinions that otherwise impact the scope of the defense by addressing conduct after warnings are issued and who warnings must be issued to.

Recent Developments: Proposed Federal Bill Eliminating Learned Intermediary Defenses

In a move that has received an amazingly miniscule amount of coverage, Representative Bob Filner (D-CA) introduced the Consumer Protection Act of 2011, HR 542, on February 8, 2011. The bill, co-sponsored by Representative Dennis Kucinich, was introduced "to eliminate the learned intermediary defense to tort claims based on product liability, and for other purposes." Currently in committee, HR 542 is deceptively dangerous in its brevity, stating only:

SECTION 1. SHORT TITLE.

This Act may be cited as the "Consumer Protection Act of 2011."

SECTION 2. LEARNED INTERMEDIARY DEFENSE.

(a) In General—It shall not be a defense to any tort claim in any court in the United States that a manufacturer of a product has fulfilled that manufacturer's duty of care when the manufacturer provides all of the necessary information to a learned intermediary who then interacts with the consumer of the product.

(b) Definition—In this section—

(1) the term "learned intermediary" means a person, licensed under applicable State or Federal law, to advise a consumer whether or not to use the product in question; and
(2) the term "State" includes the District of Columbia, Puerto Rico, and any other commonwealth, possession, or territory of the United States.

Notably, although the learned intermediary defense is generally presumed to only apply to pharmaceutical manufacturers, the bill contains no such limitation. Instead, it refers broadly to "products" and could conceivably apply to any product or, in some circumstances, sophisticated users. Further, HR 542 would govern "any tort claim in any court in the United States," thereby creating substantial preemption concerns.

Though opposition to HR 542 has been largely silent, it is unlikely the bill will make it out of committee and even more unlikely it will pass, given the current Republican majority in the House.

Recent Developments: Application to Pharmacies and Effect on Warnings Provided by the Manufacturer

Traditional application of the learned intermediary defense involves a prescribing physician and the warnings provided to that physician. However, a subset of that rule also applies to pharmacies, given their interaction with both the physician and the patient. While the majority of courts recognize application of the learned intermediary doctrine as applied to pharmacists, in recent years several states have addressed the interaction between a pharmacy, charged with determining dosage for a patient, and a prescribing physician, charged with providing a patient sufficient information to create an informed decision. This discussion manifests in two primary areas: whether a pharmacist has an independent duty to warn a patient regarding a change in dosage, and whether the pharmacist has a duty to warn the physician of dangers known to the pharmacist regarding the prescription or the appropriate dosage. The pharmacist's duty, in turn, impacts what warnings regarding dosage and usage must be included for a manufacturer to comply with its obligations under the learned intermediary doctrine.

As several courts have noted, rather than a general duty to warn, a pharmacist has a duty to warn physicians if aware of a specific danger. As noted by the Seventh Circuit, if a pharmacist "knew that the plaintiff was abnormally susceptible to a particular side effect of [a drug], it had a duty to warn her or her physician. But she doesn't allege that the pharmacy knew anything about her susceptibility, and so it had the full protection of the learned intermediary doctrine." *Walton v. Bayer Corp.*, 643 F.3d 994, 1000-01 (7th Cir. 2011).

One court has recognized that a "pharmacist was under no duty to warn the customer of the possible interaction between the two drugs under the learned intermediary doctrine. To hold otherwise would impose a greater duty on the pharmacist than on the drug's manufacturer, as the duty of extending warnings to patients concerning prescription drugs belongs with physicians." *DiGiovanni v. Albertson's, Inc.*, 940 N.E.2d 73, 76 (Ill. Ct. App. 2010). However, as addressed recently by the Alabama Supreme Court, a pharmacist may have a duty to notify a customer regarding a change in the dosage amount of a particular product. *Nail v. Publix Super Markets, Inc.*, No. 1091740, 2011 WL 1820087, at *7 (Ala. May 13, 2011). That court distinguished between warning regarding the effects of an increased dosage, a duty given to the treating physician, and a duty to notify regarding the change in dosage. "However, Nail is arguing that the pharmacist should

have told her that there was a significant *change* in her dosage of a very dangerous drug, not that Publix should have warned her against any possible harm in taking that dosage amount. Notifying a customer that there has been a change in prescription strength does not infringe upon the physician-patient relationship. Accordingly, we cannot say that the learned intermediary doctrine bars Nail's claim against Publix." *Id.* Thus, in most cases, the duty to warn regarding the effects of a particular dosage still falls to a physician, which in turn requires such warnings to be provided by the manufacturer to that physician. Warnings regarding the amount or dosage may be appropriate with regard to pharmacies.

State Court Update: Possible Exceptions

Several states, including in particular Texas, Connecticut, and Montana, have developed possible exceptions or limitations to the application of the learned intermediary defense. These exceptions can impose additional requirements on a manufacturer, including providing warnings to additional providers other than the prescribing physician and/or warnings directly to consumers, and can substantially limit the application of the defense.

Direct-to-Consumer Advertising

One extensively discussed exception or limitation to the application of the learned intermediary defense is direct-to-consumer advertising. This issue has been addressed by courts in the context of drugs or devices where the consumer is more actively involved in the selection of the drug or device (i.e., birth control, impotency drugs) than your typical situation where a doctor prescribes the treatment without input from the patient. A Texas appellate court recently articulated a direct-to-consumer advertising exception, despite earlier Texas case law to the contrary. *Centocor, Inc. v. Hamilton*, 310 S.W.3d 476, 504 (Tex. App. 2010).

The *Centocor* court, in applying the direct-to-consumer advertising exception to the learned intermediary doctrine, deviated from other Texas courts that had previously found that the learned intermediary doctrine applies even where the manufacturer distributes informational materials to the patient through health care providers. *See Wyeth-Ayerst Lab. Co. v. Medrano*, 28 S.W.3d 87, 93 (Tex. App. – Texarkana 2000); *Burton v. American Home Prods.*

Corp. (In Re Norplant Contraceptive Prod. Liab. Litig.), 955 F. Supp. 700, 708-09 (E.D. Tex. 1997), aff'd, 165 F.3d 374, 379 (5th Cir. 1999). Instead, the court found that "the premises underlying the doctrine are unpersuasive when considered in light of direct marketing to patients. The situation presented is more similar to the recognized exceptions to the doctrine, where courts considering the issue have found it was unreasonable for a manufacturer to rely on an intermediary to convey a warning, given that direct advertising and changes in the provision of health care impact the doctor's role and promote more active involvement by the patient." *Id.* at 508. The court found that because the manufacturer had made direct representations to the patient, that even adequate warnings to the doctor were insufficient. "Under these circumstances, we hold that when a pharmaceutical company directly markets to a patient, it must do so without fraudulently misrepresenting the risks associated with its product." *Id.*

Particularly concerning to manufacturers, the direct-to-consumer "advertisement" at issue in *Centocor* was not a typical advertisement intended to induce a patient to seek a prescription from their doctor. Rather, the video shown to the patient was part of a "treatment companion kit" intended for use by the treating physician to educate the patient regarding a medication the physician had already decided to prescribe. *Id.* at 486. In fact, the plaintiff was shown the video *while* she was receiving her first infusion of the drug. *Id.* As such, the manufacturer argued that the "advertisement" could not have caused the plaintiff's injuries because she was already receiving the medication at the time she viewed the video. The court rejected this argument, rationalizing that the patient received multiple infusions of the drug, and may have decided against future infusions had she not relied upon the treatment companion video. *Id.* at 511-12.

Centocor is currently on appeal before the Texas Supreme Court, and there is much speculation about whether the court will overturn the decision. Regardless of the outcome, manufacturers should evaluate the benefits of providing patient care materials to prescribers. In some instances, the risk of inadvertently waiving the learned intermediary defense will outweigh any benefit of providing the materials. All patient care materials should recite all warnings contained in the product labeling, and manufacturers should resist the urge to include patient "testimonials" or other statements that could be interpreted as persuasive rather than educational. Manufacturers should

instruct doctors that the materials are not intended for advertising purposes, but rather to assist patients with understanding their treatments.

Nullification of Warnings

A second trend limiting the learned intermediary defense is emerging where a manufacturer's statements and conduct nullify legally sufficient written warnings. In other words, the conduct of the manufacturer renders the warnings ineffective. For example, Connecticut has carved out an exception where the manufacturer contradicted its own written warnings in its statements to patients and physicians. *See Hurley v. Heart Physicians, P.C.*, 3 A.3d 892, 903 (Conn. 2010). The *Hurley* decision provides warning to manufacturers that they may be liable when their conduct and/or communications (particularly the conduct of their sales representatives) contradict a sufficient warning set forth in the product's labeling.

Expanded Duties to Warn

A third trend in limiting the protection under the learned intermediary doctrine involves the duty to warn other providers in addition to the prescribing physician. A Montana court recently addressed whether "the duty to warn as set out in the Restatement (Third) of Torts (hereafter, "the Restatement")…provides that warnings must be provided to 'prescribing and other health care providers who are in a position to reduce risks of harm' or whether the duty merely extends to the prescribing physician." *Stevens v. Novartis Pharmaceuticals Corp.*, 247 P.3d 244, 257 (Mont. 2010). The court noted:

> The realities of modern medicine increasingly conflict with the learned intermediary doctrine's underlying premises. Unsurprisingly, the doctrine is in a state of flux as it adapts to new medical practices. We need not set out the precise confines of the doctrine as it would apply to numerous hypothetical scenarios. We concur with authorities who consider the learned intermediary to be the health care professional actually responsible for making decisions related to the patient's care, especially when the prescribing physician is no longer involved with the continuing

> treatment and supervision of the patient. In these instances, the underlying rationale of the individualized relationship between the prescribing physician and the patient is truly no longer present.

The court concluded that the restatement requirement is not inconsistent with the law of Montana in a case where a health care provider other than the prescribing physician has primary care of the patient such that the warnings should be provided to that treating physician as well. *Stevens v. Novartis Pharmaceuticals Corp.*, 247 P.3d 244, 259-60 (Mont. 2010). While it is important to note that this discussion is mostly *in dicta* and was not the controlling issue on appeal, the obligation to provide warnings to physicians other than a prescribing physician appears to be a trend worth watching, and may impose an increased burden on manufacturers.

Recent Developments: Warning Compliance and Sufficiency of Warnings

As addressed above, the learned intermediary defense primarily impacts findings of proximate causation. In other words, where a manufacturer has warned a learned intermediary of a particular danger, the patient is deemed warned whether the learned intermediary passes on that warning or not. However, another issue arises where a physician was not warned of a danger and the patient develops a separate complication but claims that he or she would not have taken the medication if all the warnings had been provided—or the prescribing doctor claims he or she would not have prescribed the drug had he or she known of the danger. Whether this argument establishes proximate causation will depend on the governing state's law. For example, at least one Pennsylvania court has found that there is no proximate cause for the patient's failure-to-warn claim even where a physician "stated that he would not have prescribed" a drug if he had known of the risk of a disease required by the FDA as a black box warning, but the patient developed a separate disease the manufacturer adequately warned of. *Cochran v. Wyeth, Inc.*, 3 A.3d 673, 677 (Pa. Super. Ct. 2010). The court concluded that "a plaintiff cannot establish proximate causation where the non-disclosed risk never materialized into an injury." *Id.* at 679.

Manufacturers should be aware of this somewhat creative argument by plaintiffs, and be mindful that proximate cause is often subjective and state case law often varies drastically on the issue.

At its core, the learned intermediary defense is one of proximate causation, and it will limit potential liability for a manufacturer where a particular warning is issued, that warning is adequate, the conduct of the manufacturer does nothing to nullify that warning, and all appropriate treaters are included. As each state develops particular facets of this defense, the doctrine will continue to develop and in some instances narrow. Attorneys practicing in this area need to be prepared to address a growing trend limiting the protections of the learned intermediary defense. As noted by the court in Montana, very often treatment relationships in modern medicine are complex and can greatly complicate interactions regarding warnings. While enactment of a law such as HR 542 is unlikely, medical personnel, pharmaceutical companies, manufacturers, and their attorneys need to be aware of such complications and the trend towards limiting this defense.

Manufacturers should be mindful that any materials published, even if not intended as advertisements, could be read by courts as direct-to-consumer advertising. Many manufacturers provide "patient care" materials intended to assist the health care provider in educating the patient about their disease and their medication. Manufacturers should assess the benefit of continuing such practices with the risk that the patient care materials could obviate any learned intermediary defenses. Additionally, patient care materials should be reviewed, and any patient testimonials or other persuasive statements should be omitted. Similarly, manufacturers should carefully train and monitor their sales staff to ensure that all sales-related materials and pitches in no way minimize or contradict the warnings or other information contained in the product label.

Conclusion

The FDA's oversight powers have dramatically increased as a result of the FDAAA. Over the next few months, manufacturers of prescription medications must prepare for increased FDA oversight with respect to their product labels. The FDA's recently issued draft guidance leaves little doubt

that the FDA can and will unilaterally order changes to a drug's (or a class of drugs') labeling based upon the FDA's review of new safety data. Manufacturers must be prepared to promptly respond to such demands, as the timeline currently proposed by the FDA gives manufacturers only thirty days to provide their initial response.

Manufacturers and their counsel must also reevaluate their preemption challenges pursuant to recent rulings by the US Supreme Court. Failure-to-warn claims against generic manufacturers are preempted—claims against manufacturers of branded drugs are not. Preemption challenges in cases involving branded drugs could, in some jurisdictions, be met with sanctions or cost awards.

Clients should also be counseled to assess the benefits of providing "patient care" and related educational materials versus the risk of inadvertently waiving learned intermediary defenses. In those circumstances where the materials are deemed beneficial or even necessary, manufacturers should limit the content to information about the disease process and treatment. Patient testimonials and other persuasive content should be omitted. Sales practices should also be evaluated to ensure that all representations are consistent with the product label. Lastly, lobbying efforts may be warranted to table the proposed Consumer Protection Act of 2011, which would eliminate the learned intermediary defense in all product liability suits.

Key Takeaways

- Advise drug manufacturer clients to track safety trends and data affecting their product as well as drugs within the class of their product. They must be prepared to act quickly should they receive a notification letter, and have the data to refute any suggested labeling changes made by the FDA. Clients should proactively put into place response teams and policies and procedures for responding to notification letters.
- Counsel clients that federal law may or may not preempt state law claims of inadequate warnings in prescription pharmaceuticals. Clients must deal with the statutory incongruity between branded and generic drugs.

- Caution manufacturers about the risks of waiving their learned intermediary defenses. Courts are trending towards further limiting the defense. Manufacturers should reevaluate the benefits of providing certain "patient care" materials, and all such materials should be revised to omit any patient testimonials or persuasive statements. The conduct of the manufacturer may also nullify a properly labeled warning, and as such all sales activities must be consistent with the warnings contained in the product label.
- Manufacturers should also be mindful that some jurisdictions have held that health care providers other than the prescriber may be entitled to warnings. While the practical implications of such an expansion of the manufacturer's duties seems impossible, manufacturers should consider targeting health care providers in fields related to their core prescribing market with safety information and updates.

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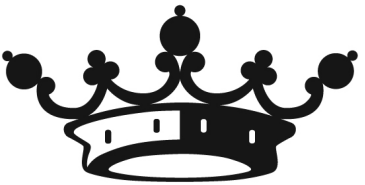

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