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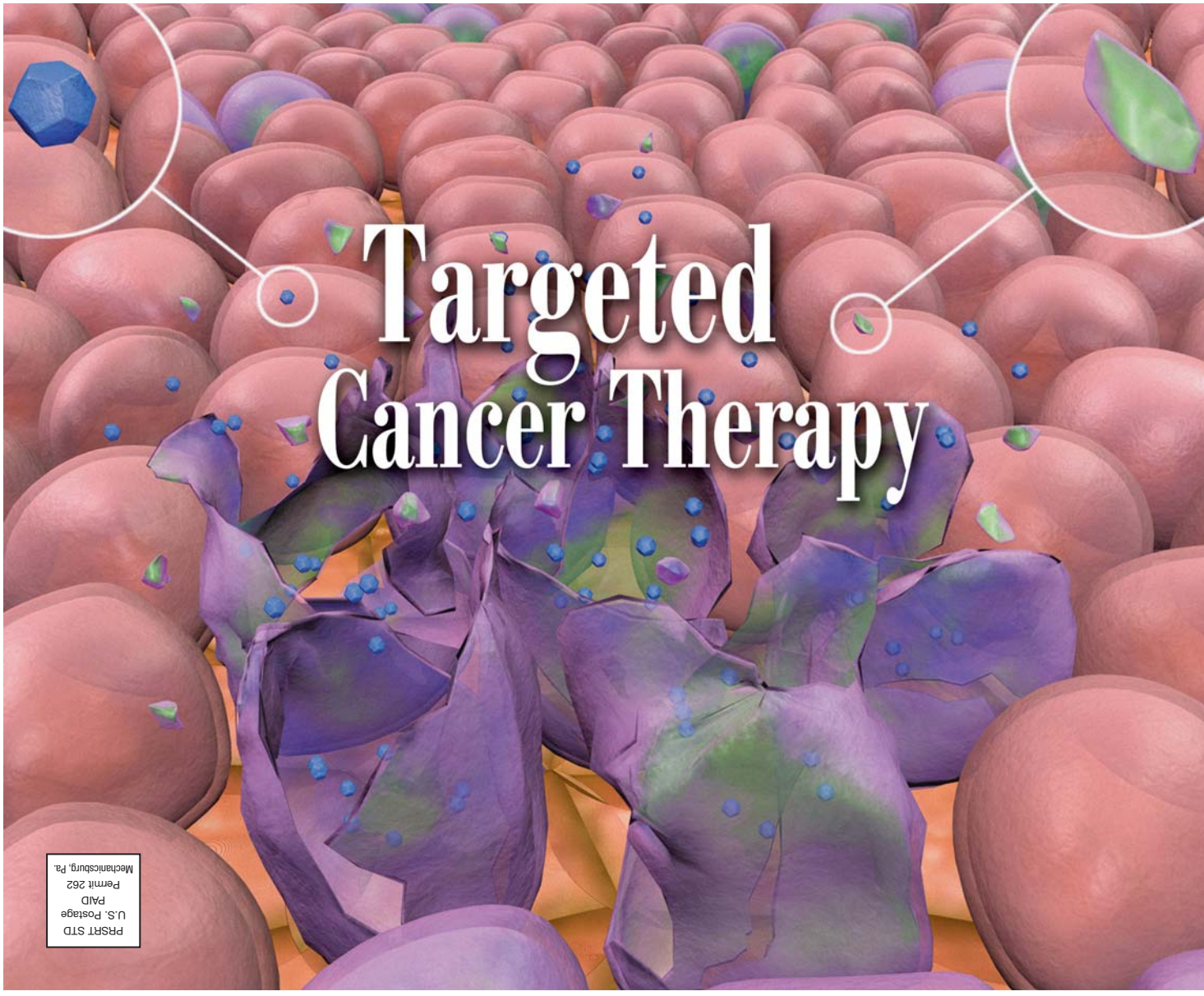

Targeted Cancer Therapy

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Approved-Labeling Defense May Gain Traction in the Wake of FDA's Pre-emption Declaration in Final Drug Labeling Rule

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Introduction

Pharmaceutical companies have long struggled with a costly Catch-22: state courts and juries can, and do, hold companies liable for patient deaths or injuries based on the omission of safety information from drug labels, yet the "missing" information may conflict with, or be contrary to, the labeling required by the FDA. Even in cases in which the drug company is ultimately found not liable, defending against such lawsuits is costly, not only in terms of legal fees and expenses, but also in terms of adverse publicity, loss of goodwill, diminished market share and stock price, as well as the distraction of key company officials and scientists from their core jobs of developing new medicines. The specter of tort liability in "failure-to-warn" cases also contributed to the evolution of increasingly lengthy, and decreasingly useful, prescription drug labeling ("package inserts" or "PIs") that attempt to disclose every conceivable warning and side effect, including the blatantly obvious (eg, "contraindicated in patients who are allergic to this drug"), and the objectively unnecessary (eg, listing of side effects observed in clinical trials where the side effect was less frequent in patients receiving the drug than in patients on placebo).

New drug labeling regulations issued by the FDA earlier this year have the potential to positively address both the tort liability and aforementioned runaway labeling problems. The new regulations are intended to streamline the content and format of prescription drug labeling in order to "make it easier for healthcare practitioners to access, read, and use [the] information…enhance the safe and effective use of prescription drug products, and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information." In addition to the specific new labeling requirements, the FDA also issued a detailed legal explanation for the position that the FDA's congressionally mandated authority to comprehensively regulate prescription drug labeling must pre-empt most state tort law failure-to-warn claims.

The New Label Look

The most visible change in drug labeling under the new regulations is the requirement for a "Highlights of Prescribing Information" section, not exceeding one-half page in space, which includes a summary of the essential scientific information necessary for the safe and effective use of the drug. Although this provision was intended to provide a useful easy-to-use summary that might be more likely to be read than the full PI, many manufacturers expressed concerns with the Highlights section. For example, some feared that this approach would force the omission from the Highlights section of important information, that the information summarized would lack the detail and context necessary for physicians to fully understand the proper use of the drug, and that practitioners would rely solely on the Highlights without reading and understanding the more detailed information contained elsewhere in the PI. Other comments criticized the Highlights section requirement because it lacks specific guidance as to what information must be included, and that as a result, competing manufacturers of same-class drugs might selectively choose information for the Highlights section in order to gain a market advantage.

The FDA addressed the comments opposing the Highlights section and rejected them based on a variety of factors, including focus group research and psychological evidence of how people take in, remember, and use large amounts of complex information, and ultimately concluded that the advantages of the Highlights section outweighed any potential disadvantages identified by commenters. The FDA also addressed these concerns by requiring that the first item in the Highlights section must be the disclaimer: "These highlights do not include all the information needed to use [the drug] safely and effectively. See full prescribing information for [the drug]." Other information required to be included in the Highlights section is as follows:

- Drug name, dosage form, route of administration, and controlled substance symbol (if applicable);
- Date of initial US approval;
- Boxed warnings (if applicable);
- Recent major label changes;
- Indications and usage;
- Dosage and administration;
- Available dosage forms and strengths;
- Contraindications;
- Warnings and precautions;
- Adverse reactions;
- Drug interactions;
- Population-specific use information (eg, use in pregnant, pediatric, or geriatric patients);
- Patient counseling information; and
- Revision date of the label.

In addition to the new Highlights section, the FDA's final rule requires numerous other changes to the look, feel, and content of prescription drug labeling. Of most significance, the product description (chemical class, physical characteristics, etc), and information on pharmacodynamics, clinical pharmacology, and clinical trial results, that previously appeared at or near the beginning of drug labels, are now moved toward the end of the PI. Clinically more relevant information (ie, indications, dosage and administration, contraindications, warnings, and precautions) are now positioned near the beginning of the PI.

It should be noted that the final rules are not uniformly applicable to all drugs. For new and recently approved drugs (approved within the past 5 years), the new labeling rules became effective in June 2006. For older drugs, the FDA will maintain the labeling rules in effect prior to the issuance of the new regulations. Older drugs for which efficacy supplements are submitted will be subject to the new labeling rules.

Pre-emption of State Product Liability Claims Based on FDA-Approved Labeling

The controversy over the proposed labeling content and format changes pales in comparison to the controversy ignited by the FDA's pre-emption statement published in the preamble to the new rules. In the preamble, the FDA addressed the Catch-22 described in the introduction of this article by noting that product liability lawsuits sometimes allege that drug makers should be held liable for failing to include certain label information that the FDA itself has specifically considered and rejected. The FDA noted that it has become aware of "several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the [Federal Food, Drug, and Cosmetic] Act." As the FDA sees it, many state courts have interpreted the FDA's labeling requirements as only a minimum safety standard, or a "floor," and have found that state law (in the form of court decisions in product liability cases) "serves as an appropriate source of supplementary safety regulation for drugs by encouraging manufacturers to disseminate risk information beyond that required by the FDA under the act." In contrast, the FDA has interpreted the labeling approved for a drug under the FDCA as establishing "both a 'floor' and a 'ceiling,'" in part because the inclusion of additional labeling information beyond that approved by the FDA "can expose a manufacturer to liability under the [FDCA], if the additional statement is unsubstantiated or otherwise false or misleading."

To illustrate its point that without pre-emption state law can put a manufacturer into an impossible legal predicament, the FDA cited a case in which a plaintiff "claimed that a drug manufacturer had a duty under California State law to label its products with specific warnings the FDA had specifically considered and rejected as scientifically unsubstantiated." As the agency noted, in such situations, inclusion of the disputed information — in order to satisfy a state court jury finding — could actually result in the drug being "misbranded" in violation of the FDCA. Obviously, a legal regime in which a drug manufacturer can only comply with one law by violating another law is unworkable and ultimately harmful to American patients. As the FDA explained, "given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective

of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug."

Based on these and other related concerns, and relating its pre-emption position to the newly finalized labeling regulations, the FDA set forth a non-exclusive list of the types of failure-to-warn claims that would be pre-empted by the FDA's authority to regulate the labeling of prescription drugs. Such claims include the following:

- Claims based on the omission of risk information from the Highlights section of the label where "the substance of [such information] appears anywhere [else] in the labeling;"
- Claims based on the omission of risk information in advertising where the substance of the information appears in the labeling and the manufacturer has complied with the FDA's "Brief Summary" requirements for the dissemination of risk information in direct-to-consumer advertising;
- Claims based on omission of risk information that are not supported by evidence that meets the FDA's criteria for inclusion in the labeling, including risks that are mere "theoretical possibilities;"
- Claims based on omission of risk information where the drug sponsor had proposed to the FDA to include the information in the labeling, but at the time the plaintiff claims it should have been warned, the FDA had not yet required the inclusion of the information;
- Claims based on omission of information in labeling or advertising, where the substance of the disputed information had been prohibited by the FDA from being included in labeling or advertising; and
- Claims based on information that is affirmatively included in the drug's approved labeling at the drug sponsor's request (except where FDA finds that the sponsor withheld material information relating to the statement).

Although the new labeling regulations gave rise to heightened focus and concern about inconsistent tort liability claims, and the FDA's pre-emption statement was published in explicit response to those concerns, it is important to note that the FDA's pre-emption position is not limited to drugs whose FDA-approved labeling uses the new format. Rather, the agency believes, and has previously argued in various court briefs, that pre-emption should apply in the context of all FDA-approved labeling.

Predictably, plaintiffs' attorneys and various aligned interest groups reacted swiftly and angrily to the FDA's pre-emption declaration, and leveled criticisms as to its substance and procedural development. However, the pre-emption argument is not a new one — drug company defendants have regularly raised preemption as a defense, but with only some success — and even the FDA's position is not entirely new, as it is derived substantially from several *amicus curiae* ("friend of the court") briefs that the FDA has filed in pharmaceutical product liability cases in recent years (although those briefs were also criticized by some at the time).

Significantly for the future, the FDA's Federal Register pre-emption statement itself is now regularly introduced in pending drug product liability cases by defendants seeking to have plaintiffs' claims dismissed. And, while the substantive legal arguments in favor of pre-emption have been relatively well developed by industry attorneys over the years, the FDA's more formal announcement of a broad pre-emption position makes it possible that courts will be required to adopt the FDA's pre-emption position without an independent evaluation of the issue. This possibility arises from the judicial doctrine of agency deference which, in its most powerful form, can require courts to accept an agency's interpretation of facts and law when such interpretation is made within the scope of the agency's delegated authority and responsibilities. There are many complex arguments for and against pre-emption, as well as deference to the FDA's pre-emption declaration, and recent court decisions continue to be mixed. Until pending pre-emption cases make their way through the appellate courts, including the strong possibility of eventual consideration by the US Supreme Court, the pharmaceutical industry will still face the uncertainty of potential labeling Catch-22s, albeit with guarded optimism that meaningful relief may be on the way. ■

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