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Justices Must Resolve Off-Label Drug Warning Predicament

By **Sheldon Bradshaw and Lisa Dwyer** (May 10, 2021, 5:41 PM EDT)

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The U.S. Supreme Court will soon decide whether to hear a case, Janssen Pharmaceuticals Inc. v. AY, involving the off-label use of drugs approved by the U.S. Food and Drug Administration.

This case has wide-ranging implications for the practice of medicine, drug-pricing and, more importantly, patient access to medically necessary and often lifesaving therapies.

In the U.S., physicians may lawfully administer and prescribe FDA-approved drugs for off-label uses — i.e., uses that are not included in the drug's FDA-approved label. The practice, which accounts for roughly 20% of all prescriptions, is both common and critical to the public health.

For some disease states, off-label uses represent the medically accepted standard of care. For individuals diagnosed with certain cancers, there is a 71% chance that their treatment plan will include the off-label use of one or more FDA-approved drugs.[1]

Timely access to medically necessary therapies often necessitates the off-label use of FDA-approved drugs. Scientific progress in certain fields, such as oncology, can outpace the drug approval process and, given the countless combinations of drugs used to treat cancer, seeking FDA approval for every combination is not practical. Relying only on on-label uses would deprive numerous patients of lifesaving medications.

Off-label prescribing serves another valuable function: It keeps drug prices from skyrocketing. Drug prices turn, in no small part, on the monumental costs associated with the FDA's new drug approval process, which requires, among other things, data from multiple clinical trials studying the specific use that will be included in the drug's label when it is approved by the FDA — i.e., the drug's on-label use.

The average cost of bringing an FDA-approved drug to market is a staggering $1.3 billion. If every use of an FDA-approved drug had to be on-label before the drug could be used, the cost of many, if not most, drugs would be astronomical.

The Janssen case, which the Pennsylvania Supreme Court ruled in last October, threatens to dramatically

alter the off-label use of FDA-approved drugs. The court held that, as a matter of state law, pharmaceutical companies must include in the labeling of their FDA-approved drugs warnings related to an off-label use of the drug.

Specifically, the court found that drugmaker Janssen was negligent because it failed to provide special pediatric warnings in the label of an antipsychotic drug that the FDA expressly approved for use in adults only. If the decision is allowed to stand, pharmaceutical companies may be sued under state law failure-to-warn theories whenever their drugs are used off-label.

As a practical matter, given the sheer number of off-label prescriptions, it is not always possible for pharmaceutical companies to know about every off-label use for every one of their drugs. Even when an off-label use is known, it is unreasonable to expect that a drug company will know the precise warnings it should add to the label if it never studied the use in question.

As for conducting such studies, given the voluminous number of required studies and their cost, it would be impractical to even try. Doing so would divert resources from the development of new, innovative therapies and inevitably increase drug prices.

There is, however, an even more significant problem with the Pennsylvania court's decision: As a matter of federal law, a pharmaceutical company may not unilaterally add warnings related to off-label uses of its drugs. While the FDA allows pharmaceutical companies to unilaterally add certain warnings related to on-label uses, the agency jealously reserves the right to decide for itself when warnings related to off-label uses can be added.

While the FDA does not regulate off-label prescribing by doctors, it does prohibit off-label promotion by drug manufacturers. The FDA considers off-label promotion to be a form of misbranding, which is a federal crime.

One reason the FDA does not allow drug manufacturers to unilaterally add warnings related to off-label uses is that the warning could have the effect of promoting the drug for that use.

Imagine if a vaccine manufacturer were to unilaterally add a warning to its COVID-19 vaccine regarding potential side effects when the vaccine is used in adolescents, ages 12-15, before the FDA authorizes the vaccine for use in that population. Such labeling could, in the FDA's view, encourage physicians to begin administering the vaccine to adolescents.

Indeed, such a labeling change would draw a swift rebuke from the FDA. But, if the Pennsylvania court's decision is allowed to stand, the vaccine manufacturer would effectively be required to do just that — to label its vaccine in a way that is prohibited by federal law simply because it has data regarding the vaccine's side effects in an off-label population.

The FDA has an interest in protecting the integrity of the drug approval process, which allows the agency, and only the agency, to decide what uses of a drug can be approved. If a drug manufacturer could unilaterally add a warning regarding an off-label use to a drug's label, then the manufacturer, and not the FDA, could effectively be deciding the drug's acceptable uses.

The Pennsylvania court's decision turns the drug approval process on its head because it requires pharmaceutical companies to do exactly what the FDA prohibits — it requires them to unilaterally add warnings regarding off-label uses to drug labeling. In further contravention of the drug approval process,

it allows judges and juries to substitute their own judgment for the FDA's.

The Pennsylvania court's ruling places all pharmaceutical companies selling drugs that are used off-label in an impossible predicament. If they have data regarding the potential side effects of a drug when it is used in an off-label population, then they can either add that warning to the drug labeling and run afoul of the FDA, or they can refrain from doing so and potentially be subject to liability for millions, or even billions of dollars, in state-law failure-to-warn lawsuits.

When federal law and state law conflict, the U.S. Constitution's supremacy clause dictates that the state law must give way. Because the Pennsylvania court would hold pharmaceutical companies liable for failing to do what federal law prohibits, the Supreme Court should take the case and reverse the decision.

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Disclosure: The authors represent pharmaceutical and medical device companies, including Johnson & Johnson and Janssen, but have no involvement in this case.

[1] https://pubmed.ncbi.nlm.nih.gov/28164359/#:~:text=Off-label%20drug%20use%20in%20inpatients%20ranged%20from%2018%25%20to,and%20'modified%20drug%20applications.