Title:
Mifepristone and the Supreme Court: The threat that could unravel regulation of drugs in the United States

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As a result of recent judicial actions threatening the authority of the Food and Drug Administration (FDA), the future of pharmaceutical regulation in the United States (US) is uncertain. In response to the US Supreme Court's federal reversal on abortion rights in June 2022, there has been a flurry of conflicting litigation at the state-level aimed at preserving or limiting abortion access depending on the political inclination of the local governments.[1] *Alliance for Hippocratic Medicine v. FDA* is a case against the regulatory Agency that seeks to restrict abortion by preventing access to mifepristone.[2] This medicine was first approved by the FDA in 2000 and it is indicated to end an intrauterine pregnancy under restrictions to assure safe use.[3] The plaintiffs argued that mifepristone should not have been initially approved, claiming that the FDA review of evidence for safety and efficacy was inadequate.[4] Furthermore, the plaintiffs assert that the Agency had no authority to enforce changes to the mifepristone Risk Evaluation and Mitigation Strategies (REMS) program to allow for dispensing by mail during the COVID-19 pandemic public health emergency and the later removal of in-person dispensing requirements of the drug. The district court ruled partially in favor of the plaintiffs seeking to undo the approval and marketing of mifepristone products. That court decision was appealed and has now reached the US Supreme Court for ultimate determination regarding the FDA's authority to regulate mifepristone.[5] While it might appear that this case is only relevant to medical abortion, the consequences of a ruling against the FDA have far wider implications that could fundamentally undermine the system that has assured safe and effective medications in the United States for more than 60 years.[6]

In a series of briefs filed to the Supreme Court in support of the FDA, pharmaceutical representatives and professional organizations have warned of the serious policy implications of

ruling against the agency in this case.[7] A supporting brief by pharmaceutical companies, executives, and investors, for example, argued that deciding against the FDA could "empower any plaintiff to challenge the approval of other drugs, regardless of how long the drug has been on the market, [based] on spurious grounds."[8] What might sound alarmist at first, the rationale for these concerns is rooted in the risks of potentially upending years of precedence on the legislatively granted authority to the FDA to rule and decide on the safety of medications based on objective and extensive review of the evidence with expert input. Notwithstanding the economic motivations from pharmaceutical companies in supporting the Agency in the case by arguing that a decision against the FDA would hinder future drug development efforts, the departure from an expert-led decision-making process toward one decided by judges is extremely concerning. Health law experts and advocates share this concern.

Federal law currently gives the FDA the authority to regulate drug safety and effectiveness. Under the American legal doctrine of preemption that prevents state law from conflicting with federal law, state law that seeks to restrict medication access on grounds of a *drug safety concern* encroaches on the Agency's legal authority.[9] This principle was exemplified in a 2014 case ruled against the State of Massachusetts when the state government tried to ban the prescribing and distribution of a then newly FDA-approved form of extended-release hydrocodone.[9] Whereas FDA has authority over final determinations on the safety and effectiveness of medical products for nationwide distribution, state governments have jurisdiction over *medical practice* laws. This tension can create legal conflicts at the blurred lines between ensuring access to approved drugs and practical issues on prescribing and dispensing of such products by healthcare providers.[9] The arguments in *Alliance for Hippocratic Medicine v. FDA* relate to questions pertaining to drug safety, not medical practice. It is worth noting that no court has ever overridden an FDA approval of a medication in the past, making the district court's decision in this case a significant and concerning shift in judicial thinking. The change in

precedence could potentially, in the words of the brief by pharmaceutical companies to the Supreme Court, signal any person to “ask a judge to undermine patient access to any drug nationwide, based on nothing but conjecture and cherry-picked publications.”[8] FDA regulates drugs throughout their entire lifecycle, and it is understood that several considerations pertaining to benefit/harm balance are considered through the approval process and post marketing assessments. Undermining the Agency’s authority also undermines the expertise of researchers and regulators evaluating relevant scientific evidence and making recommendations backed by the best available science.

Regardless of the outcome, this case is a worrisome example of the continued need to advocate for drug regulatory decision-making based on strong scientific principles. Pharmacoepidemiologists are experts in evaluating, designing, and conducting scientifically-sound studies of medication safety and effectiveness. With increased focus and attention on real-world evidence (RWE) for regulatory decision-making,[10,11] undermining the regulatory authority and expertise of the FDA could lead to the misuse and misapplication of these studies to advance the agenda of special interest groups who are not ethically bound nor have the appropriate expertise to present an unbiased picture of the current literature. Should the courts become the ultimate authority to decide on questions related to drug safety and effectiveness, there are also concerns that groups with a specific political agenda could move towards generating and presenting the judges 'evidence' that is poorly designed without rigorous scientific knowledge. Pharmacoepidemiology as a field takes pride in using state-of-the art causal inference methodology to generate trustworthy RWE on pharmaceutical products and medical interventions. While the profession and its practitioners must continue to advocate for reproducibility and transparency,[12] there is, arguably, a more pressing need to increase efforts in advocating for objective evidence-based policy-making that relies on expert input. Even though regulatory agencies are not infallible, they routinely employ the critical feedback of several

internal and external experts to inform their decisions.[13] The field of pharmacoepidemiology must reject politically-driven calls to change drug safety determinations not substantiated by thorough review by scientific experts and advocate to ensure that regulatory agencies have the necessary authority to review, approve, and amend decisions on drug safety and effectiveness to protect the public's health.

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