Mifepristone and the courts: The thread that could unravel regulation of drugs in the United States

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Take Home Messages

- Under current law, the Food and Drug Administration (FDA) has the ultimate authority to decide on the safety and efficacy of medications approved for sale in the United States.
- There is current litigation brought forth against the FDA related to the regulation of mifepristone products on grounds of alleged inappropriate safety review for approval.
- Conflicting rulings on the FDA's authority to regulate mifepristone have reached the US Supreme Court.
- Undermining the regulatory authority of the FDA could have serious consequences on the future of drug safety determinations.
- Pharmacoepidemiologists must recognize the concerns raised by industry and public health law scholars, and the field should advocate strongly for drug regulatory decision-making backed by the best available science.

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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 US District Court for the Northern District of Texas ruled in favor of the plaintiffs seeking to undo the approval and marketing of mifepristone products. That court decision was appealed in the Fifth Circuit Court in New Orleans where it was partially reversed – The court granted a stay to the FDA's approval of mifepristone but still left in place restrictions for medication access. The case reached the US Supreme Court where the US Department of Health and Human Services asked, and was later granted, an administrative stay to maintain access to the medication while the Fifth Court hears the appeal.[5] It is likely that the case will ultimately reach the Supreme Court for final determination regarding the FDA's authority to regulate mifepristone. 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. Pharmaceutical companies supporting the FDA argue that a decision against the agency would hinder future drug development efforts. Notwithstanding the economic motivations of industry, the departure from an expert-led decision-making process toward one decided by judges is extremely concerning – Health law experts and advocates from professional medical associations share this concern.[9,10] The brief filed in support of the FDA co-signed by the American Medical Association (AMA), for example, asserts that the district court ruling against the Agency ignored the extensive body of evidence supporting the safe use of mifepristone and that the court's order "relies on pseudoscience and on speculation."[10]

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.[11] 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.[11] 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.[11] 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 undermines the expertise of researchers and regulators evaluating relevant scientific evidence and making recommendations backed by the best available science. Undercutting the FDA's authority to be the ultimate decision-making body for regulating pharmaceuticals also undermines the clinicians' ability to practice evidence-based medicine that heavily relies on the approved prescribing information.

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,[12,13] 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,[14] 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.[15] The field of pharmacoepidemiology must push back and reject legal challenges to the established regulatory process for drug safety and efficacy determinations that are not substantiated by the thorough review by scientific experts.

Advocacy efforts must focus on ensuring regulatory agencies have the necessary authority to review, approve, and amend decisions on drug safety and effectiveness to protect and promote the public's health. While advocacy can take different forms, professional organizations and experts in the field can continue to express their strong support for the current pharmaceutical regulatory process. Judicial decisions can be informed by expert input like the one provided by stakeholders' briefs for *Alliance for Hippocratic Medicine v. FDA.* Public support can also be influential and patient advocacy groups have spoken in favor of the FDA.[16] A court ruling against the regulatory body can severely affect public health by making targeted drugs inaccessible to patients, limiting the prescribing conditions deemed as "safe" based on arbitrary and misleading evidence, and, ultimately, deteriorating the public trust in the well-established

and scientifically guided process of pre- and post-marketing drug reviews. Although the decision in this case will directly affect the marketing and distribution of mifepristone in the United States, other medications could be affected in the future, especially those potentially targeted by special interest groups (e.g. contraceptives, hormone therapies for gender affirming care, and HIV pre-exposure prophylaxis).[17] It is more difficult to anticipate the impacts of such a decision beyond the United States, but the case could create ambiguity for other countries that look for guidance from FDA's decisions and serve as a model for challenges to the authority of other regulatory bodies. When asked about the best approach to a thorny decision about study design or statistical analysis, epidemiologists are known for responding, 'It depends'. In this case, the consequences are clear and so is the need to publicly advocate for the FDA to remain the sole authority to regulate medications and other medical interventions in the US.

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