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Abortion Pill Rulings Will Hinder FDA Authority

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In Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration, the U.S. Court of Appeals for the Fifth Circuit has temporarily stayed the U.S. District Court for the Northern District of Texas' ruling that invalidated the FDA's approval of mifepristone.

Still, the court's decision will seriously hinder the FDA's authority with respect to how it regulates products and determines how and when they will interact with the life sciences industry — and the judicial process.

The FDA's expertise and decision making on drug safety and efficacy are under judicial attack, which will negatively affect the predictability of regulatory decisions in the life sciences industry and on industry products.

The unpredictability will create new challenges for transactions involving these products and may result in changing strategies for companies' development programs, commercial planning and product life cycle management.

Additionally, the courts' criticism of the FDA's alleged abuse of its administrative process could, if upheld, have a chilling effect on the FDA's review of product and regulatory decisions and policies, and potentially hinder approvals.

The FDA's use of real-world evidence — rather than clinical studies — to modify drug labels, including risk evaluation and mitigation strategies, or REMS, has been undermined and will hinder the growing use of real-world evidence as a basis for the FDA's administrative actions, including approval decisions.

And the district court's effort to reduce the scope of the FDA's enforcement discretion, if upheld, could substantially change the FDA's approach to enforcement and create substantial uncertainty for thousands of products currently marketed under such policies.

Overview

Over the course of less than a week, there have been significant changes to the availability of

mifepristone and its generic equivalents — progesterone blockers that, when used with another drug, can end early-stage pregnancy.

On April 7, the Northern District of Texas issued a preliminary stay with respect to the FDA's 2000 approval of mifepristone and its generic equivalents — and the changes the FDA made to the product's REMS in 2016 and 2021 to make the product more widely available to women — pending review by the Fifth Circuit.[1]

The district court concluded that the FDA's approval and changes to the REMS program, which allowed women to access the product without seeing a physician or confirming the status of the pregnancy, was arbitrary and capricious — and exceeded the FDA's authority under the Federal Food, Drug and Cosmetic Act to approve products under Subpart H and related regulations.

However, late on April 12, the Fifth Circuit issued a partial emergency stay[2] on the district court's opinion, allowing mifepristone to remain on the market.[3] The court of appeals, though, rolled back the FDA's prior relaxation of the REMS program, thus making access to mifepristone more difficult.

At the same time, the U.S. District Court for the Eastern District of Washington issued a ruling requiring the FDA to keep mifepristone on the market, under the current version of the REMS for those states that brought the lawsuit.

There is no doubt that these conflicting decisions will have a significant impact on women's access to the medical procedure of abortion and the right to determine their own reproductive health.

The Texas district court and Fifth Circuit decisions, however, if upheld, will have significant negative and far-reaching effects.

They represent a serious trampling of the FDA's authority to review and approve regulated products and determine how and when it will use its administrative process to interact with regulated industry and other potentially affected parties, as well as its expectation of the long-standing judicial policy of deference to the FDA's scientific and enforcement expertise.

These decisions undermine the core function of the FDA and, if upheld, will cause negative ripples throughout the life sciences industry — raising questions regarding the validity and staying power of the FDA's analysis of scientific information and studies, and resulting decisions.

The court rulings may also have significant implications for who can challenge an FDA approval and when such challenges can be brought.

Although the rulings relate to a prescription drug, they should not be read as applying only to drug products.

Many of the findings and analyses of the FDA's statutory authority can be applied equally to medical devices, dietary supplements and any other product that the FDA reviews, approves and has the authority to regulate, potentially making it possible to further chip away at the strength of the FDA's credibility and administrative process in the U.S. and around the world.

Several points made by the courts in the lengthy decisions are worth considering for their long-term

impact on the FDA and the life sciences industry.

Standing to Sue for FDA's Actions

The courts' discussions on which parties have standing to challenge FDA approval of a drug product is groundbreaking.

The courts basically granted standing, i.e., a right to challenge the FDA's decision, to a medical association that alleges itself and its members' practices may be affected by mifepristone side effects.

Specifically, the association alleged that patients experiencing known side effects of the drug "can overwhelm the medical system and place 'enormous pressure and stress' on doctors during emergencies and complications," and that the organization itself is affected by the FDA's actions by having to spend its resources educating members about mifepristone.

On appeal, the court specifically pointed to the FDA-approved mifepristone labeling, which directs patients to seek emergency care in the event of certain side effects, to support the proposition that there can be serious product-related complications that require physician intervention.

Relying on these known side effects, the appeals court stated that "emergency room doctors have a concrete, particularized injury since they have provided — and with certainty will continue to provide — the 'emergency care' ... specified in the [labeling]."

The appeals court also found that doctors face "enormous stress and pressure" when treating women experiencing side effects and unsuccessful chemical abortions, providing a basis for the association representing the doctors to claim that the FDA's actions significantly affect doctors' quality of life.

Finally, the appeals court found that these injuries are "traceable to FDA regulations and redressable by the court" because the FDA's relaxation of the REMS to "empower nondoctors to prescribe mifepristone ... shift[s] the cost of the drug onto ... physicians who must manage the aftermath."

The court stated,

> "FDA's actions have created a culture of chaos for emergency room physicians." ... And we're capable of redressing plaintiffs' injuries by restoring the 2000 Approval's REMS.

These decisions potentially open up the universe of potential challengers to any FDA drug approval or failure to approve a drug.

By their nature, every drug will be associated with adverse events that may require medical intervention, and there will be some category or scope of adverse events that are not known at the time of a product's approval.

The court of appeals did make a point of stating that it was not holding that "doctors have constitutional standing whenever they're called upon to do their jobs" and that it was not holding "that doctors have standing to challenge FDA's actions whenever the doctor sees a patient experiencing complications from an FDA-approved drug."

Instead, the court attempted to draw a distinction based on the certainty that "hundreds of thousands

of women will ... need emergency care" due to the FDA's actions and based on the fact that the FDA "chose to cut out doctors from the prescription and administration of mifepristone," thus creating an "exceedingly unusual regime."

Notably, the court provides no guidance on how impactful an FDA product approval, a product's side effects or even a product's lack of approval must be — e.g., thousands of patients, or tens of thousands — to consider its effects on doctors as a basis for standing.

The court also does not address whether a product's impact on the many other parties in the health care system — e.g., hospitals, nurses, ambulance drivers — would form the basis for challenge to an FDA decision. This could also open the door to an even wider breadth of actions for a wider range of products.

The decision also elevates the role of doctors above others within the health care system, by only considering that side effects will be addressed by physicians.

Notably, however, the patient agreement form does not talk specifically about doctors, but rather directs patients to seek the care of health care providers more generally.

This focus on the role of the physician and the emphasis on cutting out doctors from the prescribing decision may provide a potential argument for organizational challenges to other actions taken by the FDA and states that permit other health care professionals — e.g., nurses, pharmacists — to engage in product prescribing.

The decisions further raise the question of whether standing would ever be declined, as the appeals court did not address the district court's other bases for standing.[4]

This opens up the courts to a wide array of additional FDA challengers. For example:

- Competitors whose products will be affected in the market;
- Parents whose children will or will not be able to access drugs based on the scope of approval; or
- A broad array of patient advocacy groups whose members demand that the FDA rely on certain studies to approve a label or that more clinical information about a drug is necessary before it is released to the market.

Timing of Challenges to FDA Actions

Challenges to final agency actions are subject to a six-year statute of limitations. Typically, agency actions that are not yet final and agency actions that took place more than six years ago cannot be challenged.

On this basis, the court of appeals found that the plaintiffs could not challenge the FDA's original 2000 approval and the FDA's associated 2016 denial of the plaintiffs' citizen petition, as both took place more than six years before challenge was brought.

In coming to this decision, the court held that the FDA had not reopened its original approval decision by

modifying the REMS. The court, however, appeared to leave room for disagreement, stating, "Although a close call, we are unsure at this preliminary juncture and after truncated review that FDA reopened the 2000 [approval]."

The court, though, noted that "plaintiffs could very well prevail on this reopening claim."

The court of appeals found, however, that challenges to the FDA's REMS changes were timely — the plaintiffs had filed citizen petitions with the FDA with respect to these changes in 2019, which the FDA did not act on until 2021.

Should it ultimately be found that the FDA's REMS modifications reopened its original product approval decision, this could have significant implications for decisions with respect to a product's life cycle and label updates.

Modifications to REMS programs and drug labels more generally based on real-world product experience are not uncommon.

However, if it is ultimately determined that changes to a REMS program can provide plaintiffs a refreshed opportunity to challenge the underlying product approval and not just the REMS modification, it will chill drug manufacturers from updating labels based on real-world evidence and may dissuade the FDA from making any necessary adjustments to product labels including those subject to a REMS.

Moreover, if REMS changes permit plaintiffs to reopen the issue of the FDA's original approval decision, other changes to a product's conditions of use, including substantive labeling changes, could allow plaintiffs to essentially reach back and challenge the approval of drugs that have been on the market for decades.

Exhaustion of Administrative Remedies and Abuse of Process

While the court of appeals found that the plaintiffs had exhausted their administrative remedies based on their citizen petitions, it also found that even if they had not, the court could waive exhaustion on the basis of futility and administrative abuse of process.

Specifically, the court found that the FDA's repeated denial of the plaintiffs' citizen petitions concerning mifepristone indicated that it would be useless to raise further challenges to the original approval via the citizen petition process.

The court also found that the FDA abused its own administrative process by failing to follow its own regulations requiring it to respond to citizen petitions within 180 days of receipt. Here, it took the FDA 14 years, in one instance, and two years, in another instance, to respond.

As the FDA has often used the failure to exhaust administrative remedies as a gate to delay or preclude judicial review, the ruling may cause the FDA to defend its decisions in court without having the benefit of administratively considering the issue when plaintiffs are able to make out a futility argument, and will give persons critical of FDA decisions a quick pathway to judicial review.

It may also cause the FDA to change the way that it addresses citizen petitions. As the FDA frequently well exceeds the time allowed for responding to citizen petitions, this may cause the agency to either speed up its review of citizen petitions or issue quick denials in order to avoid having a delayed response

held against it in connection with its substantive decisions.

Judicial Deference to Agency Expertise

In several places in the decisions, the court of appeals and district court undercut the long-standing judicial deference provided to agency expertise.

The Fifth Circuit found that the agency acted arbitrarily and capriciously by failing to examine relevant data when making its 2016 REMS changes. Specifically, the court found that the FDA improperly "eliminated REMS safeguards based on studies that included those very safeguards."

According to the court,

> The fact that mifepristone might be safe when used with the 2000 Approval's REMS (a question studied by FDA) says nothing about whether FDA can eliminate those REMS (a question not studied by FDA).

Moreover, while the FDA did study the safety consequences of removing certain aspects of the REMS, in the court's opinion, this was not sufficient because these were studied in isolation and did not study the REMS changes as a whole.

The court further found that the FDA essentially undercut its data collection on the product's safety by eliminating the requirement that nonfatal adverse events be reported by prescribers.

The court stated that it is "unreasonable for an agency to eliminate a reporting requirement for a thing and then sue the resulting absence of data to support its decision."

While not addressed by the appeals court, the district court held it was improper for the FDA to approve mifepristone under the FDA's regulations that are applicable to products intended for serious and life-threatening illnesses where the product provides a meaningful therapeutic benefit over existing treatments, called Subpart H.

Specifically, the court found that pregnancy is not a disease and use of the drug is not a therapeutic treatment for a disease.

Similarly, the district court stated that the FDA's interpretation of its regulations under Subpart H did not warrant deference because the regulation was not ambiguous, nor was the FDA expertise needed for interpretation of the language at issue, i.e., the court could interpret the word "disease" as easily as the FDA.

The district court also cited medical literature and data that chemical abortion is less effective than surgical abortion, and therefore concluded mifepristone could not be a more effective treatment.

These discussions signal the continued slow erosion of judicial deference to the FDA's scientific and medical expertise to identify, analyze and apply a wide variety of scientific and medical data as a basis for its decisions.

Comstock Act

One of the significant issues in the case has to do with the Comstock Act, which prohibits the knowing mailing or delivering of any "article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion."

The court of appeals appears to imply that the Comstock Act may not only make the mailing of mifepristone illegal, but also make the mere distribution of mifepristone as part of the regular drug supply chain illegal, regardless of the fact that the product was approved by the FDA.

The court, however, made a point of stating that the speed of its review does not permit a "conclusive exploration of the topic." However, to "the extent the Comstock Act introduces uncertainty into the ultimate merits of the case, that uncertainty favors the plaintiffs" — i.e., the organization challenging the product's approval.

Not only may this have implications for the future of mifepristone's distribution, but, if it is determined that the Comstock Act does prevent the distribution of mifepristone, it may also signal to lawmakers that politically disfavored products that are approved by the FDA can be blocked through the passage of a Comstock Act — like statute, potentially introducing political whims into a process that is intended to be based on the scientific and clinical merits of a product.

What's Next?

While the appeals court decision represents a partial win for the FDA, the FDA's fight is not over.

The Fifth Circuit order requires the FDA to reinstitute the original 2000 approved REMS. Both the government and Danco Laboratories, the mifepristone sponsor, have filed in the U.S. Supreme Court for emergency stays of the April 7 preliminary injunction order issued by the Texas district court.

In its request for an emergency stay to the Supreme Court, the FDA states that the lower court orders "unleash[] regulatory chaos by suspending the existing FDA-approved conditions of use for mifepristone."

The Fifth Circuit will also begin the longer process of reviewing the district court's decision on the merits — the Fifth Circuit previously only decided the government's emergency motion for a stay pending appeal.

Although not certain, this review will likely be undertaken by a different panel of appeals court judges than the one that reviewed the emergency stay motion.

This merits panel will not be bound by the initial assessments made by the motions panel and will reach its own conclusions about the merits of the district court's order.

Merits Panel Issues

The following issues, while not addressed by the motions panel, may be addressed by the merits panel, in addition to other issues raised in the merits panel order.

FDA Required Conditions of Use

When approving a drug, the FDA must specify the product's approved conditions of use — e.g., what the

product is approved for, how it should be used, limitations on use.

In some cases, the conditions may have been part of the clinical trials supporting the product's approval; in other cases, the conditions may be required by the FDA or volunteered by the drug sponsor.

Frequently, clinical trial enrollment prerequisites are more stringent than the FDA's conditions of use because of the need to ensure homogeneity within the tested subject population and because of inherent safety and efficacy uncertainties for investigational products.

In the case of mifepristone, the district court faulted the FDA for not requiring the tighter controls used during clinical trials for the commercial use of the product, finding the FDA's failure to require the tighter controls to be arbitrary and capricious.

This reasoning should cause drug sponsors to carefully consider the design of clinical trials that are used to support product approval. Where scientific prudence may call for tight study subject inclusion and exclusion criteria, this should be weighed against the potential real-world use of the product and the potential for label restrictions in the future.

The FDA's departure from clinical trial conditions — e.g., indications, patient populations, REMS and other restrictions — may make a product a target for challenge once marketed.

FDA Enforcement Discretion

The district court had substantive negative views on how the FDA exercises its regulatory discretion. Under the 1985 Supreme Court case Heckler v. Chaney, the court held that the FDA's decision to pursue an enforcement action was a matter that was committed to agency discretion.

The FDA frequently exercises its regulatory discretion, with respect to both the regulation of entire classes of products or manufacturers and individual product or company matters.

According to the Texas district court, however, enforcement discretion is intended to be appropriate for one-off decisions by the FDA; it is not to be used as a basis for not enforcing an entire part of the statute.

This ruling could significantly undermine other FDA enforcement discretion policies in which the FDA has stated it will not take action against whole categories of regulated products including over-the-counter drugs, dietary supplement ingredients, wellness devices and laboratory-developed tests.

The court made clear that the FDA cannot abdicate its responsibility wholesale for enforcing the Federal Food, Drug and Cosmetic Act and related acts.

FFDCA Zone of Interest

As part of the district court's standing decision, the court concluded that the FFDCA is intended to protect the safety of physicians' patients and the patient-physician relationship.

While the FFDCA is intended to protect public health by ensuring that medications are safe and effective, it does not specifically address the regulation of the patient-physician relationship.

Notably, the FDA and the FFDCA carefully stay out of the patient-physician relationship and the practice of medicine, e.g., by permitting the off-label prescribing and use of approved medications by physicians.

The Texas district court decision is a new interpretation of the purpose of the statute. It may have policy and legal implications on future decisions by the FDA and how courts interpret the FDA's decision-making rationale, notwithstanding the historical regulation of the patient-physician relationship and informed consent for treatment under state laws.

Notably, this part of the decision was not addressed by the court of appeals and thus was not overruled.

Conclusions

The exact impact of the current Texas and Fifth Circuit decisions is yet to be seen. Although the decisions relate to a single product, they could have broad implications for the life sciences industry as a whole and how the FDA regulates products.

Despite the ultimate outcome of a permanent injunction action, the underlying rationale for the courts' decisions and the associated dicta, if not struck down, may endure, providing ammunition for future challenges to FDA actions.

Accordingly, the exact language and basis of future appeals decisions will be of significant importance on these broader issues of the FDA's authority.

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[1] https://fingfx.thomsonreuters.com/gfx/legaldocs/myvmojgodvr/ND%20Texas%20Abortion%20Pill%20Ruling%202023-04-07.pdf.

[2] https://storage.courtlistener.com/recap/gov.uscourts.ca5.213145/gov.uscourts.ca5.213145.183.2_1.pdf.

[3] Notably, it appears that the 2019 approval of the generic version of mifepristone is still preliminarily enjoined, though this was not directly addressed by the Fifth Circuit. However, given that the 2000 reference listed version of mifepristone can currently be marketed under the original 2000 approval (assuming necessary labeling changes are made), there may be an argument that a generic product, with labeling the same as the 2000 reference listed drug, could also be marketed.

[4] In addition for the bases for the court of appeals holding up the plaintiffs' standing, the district court also found standing on the basis that its physician members are prevented from practicing "evidence-

based medicine" and are exposed to an increased risk of malpractice and liability claims, with accompanying higher insurance costs, because there is a lack of "full" information about the drug due to FDA's failure to require collection of all adverse event information, preventing full patient informed consent and harming the patient-physician relationship.