Life sciences companies and the risks posed by the mifepristone litigation

Welcome to DLA Piper's *At the Intersection of Science and Law* podcast. In this episode, a cross-disciplinary team of FDA regulatory lawyers and life sciences litigators discuss the implications of the mifepristone litigation for life sciences companies as it pertains to citizen petitions, FDA approvals, and strategies manufacturers might consider going forward.

Bethany Hills: I'm Bethany Hills, Vice Chair of the DLA Piper FDA regulatory and compliance practice, and I focus my practice on the intersection of FDA, healthcare, and compliance regulations for the life science industry. I'm joined by Whitney Cloud, a litigation and appeals partner in our Philadelphia office, specializing in multi-plaintiff disputes involving government enforcement or regulators. She was a complex crimes prosecutor and Chief of Appeals at the US Attorney's Office in Delaware prior to joining DLA Piper. Since joining DLA, she helped initiate the Dobbs Task Force and she regularly advises clients on implications of appellate decisions like Dobbs in crafting litigation strategies.

Katie Insogna is a partner in our DLA Boston office. She's co-chair of the pharmaceutical and medical device subgroup, and regularly represents life sciences companies in high stakes litigation. In addition to her litigation practice, Katie counsels clients on research and development, risk management, and other compliance issues.

And Jarred Reiling, of counsel in our New York office. He's part of our FDA regulatory practice group. He began his legal career at FDA and left FDA to serve as a federal law clerk in the 11th Circuit in the Southern District of Florida. During his career, he's helped market leading companies in the pharmaceutical, medical device, tobacco, and other sectors with regulatory strategy, compliance, and related investigations and litigation.

On this episode, we're focusing on the impact for life science companies arising from the litigation challenging FDA's approval of the abortion pill Mifepristone, and changes to Mifepristone's post-market restrictions. Although the litigation itself is still evolving with major updates at a regular cadence, we are already focusing on what life sciences companies can start to do to prepare themselves for future litigation challenges to other FDA approved medication.

So where do we stand right now, Whitney?

Whitney Cloud: So Bethany, this case started as a preliminary injunction brought by individual and associated anti-abortion medical providers in federal district court in Texas before Judge Matthew Kacsmaryk. The plaintiffs were seeking to rescind FDA approval of the abortion pill Mifepristone, which is one of the drugs in a two-drug regimen that facilitates a medical abortion. FDA first approved Mifepristone back in 2000, but it's changed the post-market restrictions to Mifepristone over the last seven years, making it easier to prescribe and obtain the pill, and also extending the approved use of the pill, through the first 10 weeks of a pregnancy.

The FDA's post-market changes achieved new significance following the Supreme Court's Dobbs decision last year, which unwound the federal constitutional right to abortion and sent that issue back to the states. So before coming to federal court, several of these plaintiffs actually challenged the initial FDA approval and a few of the post-market restriction changes through citizens petitions to the FDA and those petitions were pending for many years before ultimately being denied.

As everyone likely knows by now, on April 7th, Judge Kacsmaryk issued an order effectively negating initial FDA approval of Mifepristone, but he gave the FDA and the intervener, Danko, who manufactures Mifepristone, seven days to appeal his decision. FDA and Danko did appeal that decision and asked the Fifth Circuit to issue a stay of Judge Kacsmaryk's decision. The Fifth Circuit issued a partial stay, which would have essentially returned prescription of Mifepristone to pre-2016 levels, making it much more challenging to prescribe and obtain. And again, the government and Danko appealed that decision this time, petitioning the Supreme Court to reconsider the stay.

On April 21st, the Supreme Court issued a stay of Judge Kacsmaryk's decision in its entirety in a seven to two order with only Justices Alito and Thomas dissenting. So what all that means is that Mifepristone can continue to be prescribed and distributed as it was before April 7th, which is crazy to think was only a few weeks ago. So now a briefing on the merits of Judge Kacsmaryk's decision is going to be before the Fifth Circuit. An oral argument is set to take place on May 17th, but regardless of what the Fifth Circuit does, the case is pretty certain to end up back before the Supreme Court in the 2023 to 2024 term. So, there will continue to be a fair amount of uncertainty as to the ultimate fate of FDA's approval of Mifepristone until likely sometime next year.

Bethany Hills: That's great, and one of the things that we'd like to really get into is how did we actually get here? How did the plaintiffs really bring this case and what are some of the key issues? Katie?

Katie Insogna: Thanks, Bethany. It's fascinating how the standing issue came before this court. As Whitney said, the plaintiffs in this litigation are physicians and associations of physicians. Typically, in standard litigation involving medications, a patient uses a medication, suffers an adverse event, and sues for damages. Here, we don't have those patients suing. We have doctors suing because they had to treat patients who use the medication and those patients had an adverse event. Either it failed to work completely, or they suffered some other side effect.

That is an unusual argument for standing. And in addition, we see organizations suing, alleging that they can bring this lawsuit against FDA because they had filed citizen petitions, and as a result of that effort, their resources were diverted away from their standard operating and supporting of physicians.

Now, citizens petitions hold a familiar role in many litigations. Oftentimes FDA will have confronted some form of the issue through a citizen petition and that becomes a linchpin argument when we get to preemption in litigation. But here, if standing is affirmed, we can expect to see a wider range of litigants in federal court because they have used the citizen petition as a springboard to further litigation standing.

Bethany Hills: One of the key things that's clear from this litigation is that some of the challenges to FDA's authority in these cases have broader ramifications for life sciences companies. For example, the accelerated approval program could face criticism and challenges and even be targeted with new litigations.

Mifepristone was approved by FDA in 2000 under the accelerated approval program, which at the time was operating under a set of regulations issued by FDA in 1992. Congress formalized the accelerated approval program in statute in 2012 and, as of 2022, at least 270 drugs have been approved by accelerated approval pathway. Meaning, earlier approval of the drugs to treat serious conditions and fill an unmet medical need, but based on a surrogate endpoint.

Between 1992 and 2010, 40% of these Subpart H approvals were in HIV, 35% in cancer, and 25% in rare diseases. But between 2010 and 2020, a whopping 85% of the approvals using the accelerated pathway are for oncology indications. While the required confirmatory studies are not a key issue in the current litigation, approximately 15% of drugs approved through this accelerated program have been on the market at least 10 years without completing FDA's required confirmatory post-approval studies.

Accelerated approvals have become a critical regulatory pathway for cell and gene therapies, and also for rare disease treatments that need to leverage surrogate endpoints. We certainly predict the FDA will be far more cautious in using the accelerated approval program going forward, and this could have significant impact on the availability of life-saving therapies being available.

Katie, I know you've dug into the clinical trial issues raised in this litigation, could you share with us what you found?

Katie Insogna: Absolutely. This is a troubling argument for life sciences companies that the plaintiffs are putting forward. So, at bottom, the court went and scrutinized the clinical trial protocols before approval and compared those clinical trial protocols with the label and found a mismatch. And that mismatch is what drove the court's conclusion that FDA's approval was, in part, arbitrary and capricious. But what's interesting is that it ignores smaller factual nuances in this case, with this specific clinical trial. But also the larger realities of pre- approval clinical trials, generally. So here, there were protocol provisions, and I'll just give you one example.

The patients who received the medication were required to be monitored for so many hours after ingestion. And that requirement was then not part of the label after it was approved. But what the court didn't grapple with and what wasn't addressed in the briefing is that the monitoring period, preapproval, was imposed because the trial included a second medication that was taken at the same time that carried, at the time, they believed cardiovascular risks.

So, the post-ingestion monitoring period was driven by that medication's cardiovascular issue, but when the medication was approved, the protocol did not contemplate use of that companion medication, so as a result, the waiting monitoring period wasn't necessary. But that's an issue that was never addressed in the briefing or before the court, and it just goes to show how factually specific this inquiry would get.

But beyond this small example, the larger issue is that clinical trial protocols are designed for a variety of reasons: to ensure efficacy, to protect safety of patients taking a medication that hasn't yet been approved, but it's also designed to protect against risks in clinical trials like confounding and other things that can undermine the validity of the data that's received. And it's, the difference, that again, the court didn't grapple with, but if the court embraces this clinical trial mismatch as a potential avenue for undermining approval, that is going to put life sciences companies at risk, because as we all know, clinical trial protocols differ from the final label for a variety of reasons. And if that's enough to undermine approval, a lot of medications could be on the chopping block.

Bethany Hills: Thank you. That's a really interesting issue, and another area that we've been looking at. I know Jarred, you've really brought your regulatory expertise in assessing the post-market safety restrictions that a company accelerated approvals, and also looking at FDA citizen petition process, both of which are clearly taking center stage in this litigation. Can we get your thoughts on this?

Jarred Reiling: Yes, thanks Bethany. I'll start with the changes to post-market restrictions and how they came about in 2016. So, the government's latest brief to the Fifth Circuit outlines this pretty clearly. The sponsor applied for adjustments to the drugs conditions of use, and the REMS, which is also known as a risk evaluation and mitigation strategy. FDA approved those applications for those adjustments in 2016. The government says in its brief that FDA's approval followed a comprehensive review of the proposed modifications that considered “20 years of experience with Mifepristone, guidelines from professional organizations here and abroad, and clinical trials that have been published in peer reviewed medical literature”.

The 2016 modifications involved three aspects. The first were the conditions of use. FDA increased the gestational age limit from seven to 10 weeks, reduced the number of required in-person clinical visits from three to one, and allowed certified healthcare providers licensed to prescribe drugs under state law, rather than only physicians, to prescribe and dispense Mifepristone.

FDA relied on over two dozen studies to support those adjustments. The second area is the approved dosing regimen. Here, FDA reduced the amount of Mifepristone, from 600 to 200 milligrams, increased the amount of Misoprostol, and changed the route of administration of the Misoprostol. These changes weren't really discussed in plaintiff's challenge or in the district court's order.

And the third area was a narrowing of the adverse event reporting requirements. So, previously, prescribers agreed to report certain adverse events such as blood transfusions to the drug sponsor. FDA basically brought Mifepristone into the realm of other prescription drugs where information on non-fatal adverse events would be collected and reported through periodic safety update reports and annual reports that sponsors are required to submit to FDA.

The government asserts that this change was supported by over 15 years of adverse event reporting. In terms of implications, I would characterize the regulatory record here as relatively strong. I'll dive into real-world data and real- world evidence later in our discussion, but for now, I'll say that the 2016 modifications primarily focused on safety, and safety is the area where FDA has utilized real-world data and real-world evidence the most.

While pharmaco-vigilance is always a component of a sponsor's, post-market obligations, there is a difference between compliance and what I call a step beyond that: collecting, analyzing, and reporting safety information, not only to satisfy regulatory requirements, but leveraging real-world data and real-world evidence to inform long-term strategies.

Because real world data comes from a variety of sources, including EHR, medical claims data, and digital health technologies. There are opportunities to maximize the sponsor's knowledge base through innovation vis-a-vis the patient experience and community partnerships. Of course, there are parameters to consider when creating these sorts of

programs, but the possibilities to do so while minimizing risk are there and are something that we see in varying degrees and forms across the industry.

Turning to the citizen's petition issue. Typically, if there's a citizen's petition focused on a particular decision, FDA will consider the timing of responding to that petition in tandem with its confidence in making the ultimate decision at issue. That's why FDA will sometimes defer action on a citizen's petition. FDA will defer its ultimate decision on a citizens petition rather than outright deny it within the statutory timeline because it wants to ensure confidence in the ultimate decision. There's definitely a narrative in this case that this reflects an opportunistic agency decision-making and taking a step back in thinking about the process from FDA's perspective, though, I'll say it depends on the circumstances.

And that approach being dependent on the circumstances, is consistent with how most federal courts have approached providing injunctive relief when a federal administrative agency misses a statutory deadline as well. Arising out of the DC circuit, most courts will apply a set of factors, which are known as the TRAC factors, to weigh whether to provide injunctive relief and what I'll call agency failure to act cases.

Named from the case, Telecommunications Research and Action Center v. FCC, some courts follow the TRAC factors to determine whether an agency's delay is unreasonable. Under the TRAC factors, courts will examine: whether Congress has set any deadline or timeframe for the agency in the relevant statute; whether the Agency's delay implicates any public health danger; the plaintiff's interests prejudiced by the delay; the agency's competing priorities; and whether the agency has treated the plaintiff any differently than others.

One of these factors is what I call agency naughtiness, or in the language of court precedent, "agency impropriety lurking behind agency lassitude." This factor examines the circumstances around the agency's delay. For example, in one DC Circuit case, FDA failed to comply with 180-day deadline for 23 generic drug applications.

FDA was experiencing what it called a personnel crisis, and that combined with the fact that allowing the generics manufacturer in that case to essentially skip the line through litigation, brought the court to decline to provide equitable relief even though FDA violated the statutory deadline. In another generics case, 15 years later with the same 180-day deadline involved, a judge in DC Federal court compelled FDA to take appropriate action consistent with the FDCA, which essentially meant to decide the application.

There FDA had informed the applicant it completed review of the application after almost 400 days, which violated the statutory deadline, but because it was complex, FDA was deferring its decision. But after 600 additional days, it still hadn't taken action. In that case, the court pointed out that FDA scrutiny of the application placed the applicant in an untenable position by acquiring a showing that the agency itself recognized wasn't feasible. There's a circuit split in applying the TRAC factors. Some circuits apply them,

some find them informative, and others simply don't. The Fifth Circuit, which the Texas district court sits in, in this case, typically finds them informative. But the TRAC factors didn't apply here because this wasn't a failure to act case.

But it's interesting because if you look at the first page of the district court opinion, your eyes will go to the bolded text where the judge points out that it was 6,000 days since the citizen petition had been decided. So, it was clearly a factor. But here what the court did was rely on its inherent equitable jurisdiction similar to what a district judge did in a case involving a citizens petition in the district of Maryland that I'll touch on in a bit.

Whitney Cloud: Jarred, can I jump in and ask you, based on your discussion of the REMS and the process in the last seven years for the FDA approving post- market changes. What's your take on the fifth circuit's split-the-baby decision where the Fifth Circuit said, well, we're not going to stay approval of Mifepristone completely, but we are going to stay everything that happened after 2016.

Jarred Reiling: Yes, I think the most important thing to think about is the position that a court is in when it's deciding emergency injunctive relief, such as a request for a stay. It has to digest a record very quickly. It has to digest a lot of complex arguments very quickly. And, I think the fifth circuit was trying to give both sides a little bit of what they wanted, because disrupting the status quo is a really big deal. I think courts are really reticent to do that in providing injunctive relief.

So, I think it was a way to grapple with the standing issue in a way to say, okay, we can exercise equitable tolling. We'll give the plaintiffs a break in terms of not filing directly on time when it comes to the 2016 changes and beyond. But I think the court did really struggle with doing the same thing for reversing a decision that was made decades ago.

Bethany Hills: Thanks Jarred, and thanks Whitney for that great question. Have we seen similar challenges to FDA decision making outside of this very controversial topic area? Has FDA ever had this type of challenge and intervention from a court before? Whitney?

Whitney Cloud: So, back in 2014 there was a different type of challenge to FDA approval, but it came in the form of state regulation. So, Massachusetts passed an emergency order attempting to ban an FDA approved hydrocodone analgesic, and the manufacturer pushed back, claiming that Massachusetts state law was preempted. And ultimately, pretty quickly, the district court readily agreed striking down Massachusetts emergency order, and the litigation ended early on.

I think post-Dobbs, more people expected to be there to be interaction between state laws and certain federal laws protecting abortion in a limited manner. But that dynamic played out a little bit at the beginning of the fall, but so far hasn't really played out. So, it is interesting to see this rise of individual and as Katie was talking about associational groups trying to challenge FDA approval in a different fashion.

Bethany Hills: Yeah. And we've seen a number of criticisms of the accelerated approval pathway recently, and there's been some really high-profile cases that have called that pathway into question. Jarred, do you have some thoughts on that?

Jarred Reiling: Yeah, definitely. Thanks, Bethany. I mean, I think it's definitely not novel for there to be questions or public responses to FDA decision-making. I think that's something FDA is used to dealing with. But as you point out, Bethany, over the last few years we have seen a real focus on the accelerated approval pathway with an Alzheimer's medication in 2021, a fentanyl medication in 2018, and FDA's withdrawal of a preterm pregnancy drug earlier this year.

Two other areas too that I think we've seen challenges to FDA decision-making. One is in the Orphan Drug Act context. So, in 2021, we saw a successful challenge to FDA's approach to orphan drug market exclusivity, which hinged on the key question of whether the Orphan Drug Act prevents FDA from approving another applicant's same drug for the same disease or condition.

In full disclosure, I was on the litigation team for one of the parties in that litigation. And there FDA approved a drug for treatment of a disease in adults and later granted approval to another manufacturer for the treatment of the same disease in children. The 11th Circuit essentially unwound the pediatric drug.

And interestingly, FDA addressed the ruling and the Federal Register essentially rejecting it.

Another area is the use of citizens petitions to drive outcomes. The use of FDA Citizens petition process has been robust over the years, and every once in a while, it captures public attention. One example involved allegations that drug manufacturers were using the citizens petition process to delay the availability of competitive generics. Another example in the tobacco world involved the ban of menthol in cigarettes. Several public health organizations filed the citizen's petition urging FDA to issue a rule to ban menthol in cigarettes. After years of not responding, the agency kept issuing a deferral, essentially. The public health organization sued, resulting in FDA voluntarily complying by answering the petition and issuing the rule.

Bethany Hills: One of the things that you just mentioned, Jarred, I think is really interesting. Particularly in the Orphan Drug Act litigation. Essentially, FDA narrowly interpreted the court's decision there, saying that it only applied to that particular court case, that particular drug, and those particular facts, and that otherwise FDA would continue applying its previously applied assessment and analysis on how it would apply the Orphan Drug Act.

And I think that's an important thing to think about when we think about the future ramifications of this particular case, is that there is for sure being set up a dynamic between the courts and the federal agencies and of course Congress.

So, this is an area that we all are watching really carefully to see what the potential ramifications might be.

Jarred Reiling: Just to react to that. That's also the big question of what other courts are going to do with this decision. Is it narrowed to this particular circumstance or are there concepts or principles that can be applied to other indications, other drugs in other contexts?

Whitney Cloud: I think Jarred raises a great point of what are going to be the ramifications of this decision. And the key thing to think through in terms of what's to come is that the Supreme Court is ultimately not going to issue its opinion until sometime in the 2023 to 2024 term, and likely not till sometime in 2024.

That said the Supreme Court could easily just rule on standing. Katie brought up earlier that the standing implications of these groups challenging FDA approval, are enormous. And if the Supreme Court wants to undo the decision without getting into the merits of what happened to the FDA and whether it's possible to stay approval of an FDA drug 20 some years later, the Supreme Court could just issue a ruling on standing.

But that doesn't change the potential ramifications of Judge Kacsmaryk's decision, because ultimately, he gave litigants a bit of a roadmap as what to do in terms of bringing citizen petitions and also challenging certain FDA decision- making and processes that are vulnerable to litigation. I think that everybody on this podcast has touched on.

Bethany Hills: And one of the things we've been thinking about, particularly in our regulatory practice, and Jarred, I know we've spent a lot of time noodling over this in our discussions, is what would we be advising companies to do going forward? How do they anticipate these issues and what kind of contingency planning should companies be thinking about when they're engaging with FDA in an approval process, knowing that there are these vulnerabilities that could come up in the future, and particularly they may come out more frequently now based on this litigation?

Jarred Reiling: Yeah, I think, you know, companies already in the pre-market process, engage in a really strong dialogic exchange with FDA in identifying the areas of strengthening an application with respect to safety and efficacy, and also how to grapple with areas that are more challenging. How do we design clinical trials to address these concerns or really understand them given the data that we have? Coming out of those clinical trials, how do we make the best of what we have to ensure that we have safety for patients and also efficacy of the drug for the approved indication.

There are some strategies that FDA engages with manufacturers to mitigate those concerns. REMS is a perfect example of that. And I think once a manufacturer receives an FDA approval, there are also a lot of post-marketing requirements that a manufacturer has to comply with. And typically, once FDA approval is received, I think there's a perception among manufacturers that that decision will be protected. And that's what courts have been doing in terms of providing deference to FDA scientific judgment and not really unwinding or digging into what I'll call second guessing FDA scientific judgment in the application process.

I think if there's a momentum built out of this decision to encourage judges to continue to do that more then I think the takeaway from manufacturers is to really just amplify probably what they're already doing and be more intentional from the beginning about potential challenges or second guessing that may happen along the process.

I talked earlier about real-world evidence and strategies that companies can engage with to amplify their knowledge base. What creative ways can companies engage, and the buzzword for this is patient centricity, but what are ways that companies can engage with healthcare providers, with patients, with interested organizations involved in a particular disease state, to really engage in a discussion about the way the world is really interacting with a sponsor's medication. The good that it's doing, but also areas for improvement. I think really becoming vigilant about that is I think the biggest takeaway for manufacturers.

Whitney Cloud: I love the use of patient centricity, and I also learned a new word, dialogic, so...

Jarred Reiling: That that comes from my husband. He's in theater, so the credit goes to him for that.

Bethany Hills: And what are some other ways that companies are trying to protect themselves? Katie, I know you've been looking into this.

Katie Insogna: Yeah, we're seeing other litigations stemming from this in a way that perhaps folks didn't expect. For example, the generic manufacturer of Mifepristone, in light of the district court decision, proactively sued FDA. The suit effectively seeks to force FDA to follow specific preset procedural steps before declaring its medication unapproved or withdrawing it from the market. It's certainly difficult for ANDA holders when the NDA that it's premised on is revoked but it's unusual to see such proactive litigation happening in parallel as the NDA product is subject to current court scrutiny. I think typically the ANDAs wait and see and react on the back end. But in this case, we're seeing proactive litigation to protect themselves, and I think that this is just the beginning of litigation involving FDA and the approval process.

Whitney Cloud: Can I touch on something that Katie just said, which is that, another thing that is fascinating about this Mifepristone litigation, which remember, the key decisions in the Mifepristone litigation have all come in the space of three weeks. But one key decision that we didn't even talk about yet is a decision out of Washington.

So, as this litigation was going on in Texas, literally within the same hour of Judge Kacsmaryk's decision coming down, a court in the Eastern District of Washington issued its decision saying, in response to 17 states and the District of Columbia, asking the court to enforce FDA approval and not change any of the post-market restrictions. That court ruled in favor of those plaintiffs, which left the federal government and quite a few states in a bit of a quandary as to what is the effect of these dueling decisions?

So, not only, as Katie just raised in a great way, is this an active market in terms of court decisions for generics and for the brand manufacturers, but it's also raising questions of what is the effect of dueling federal court decisions? What are the effects of dueling state and federal court decisions? I think these are some of the consequences that we expected to see post-Dobbs. But it's just come in the form of a different type of challenge. And it's having much more significant ramifications for broader life sciences companies than I think we were expecting to see if just the challenges regarding surgical abortions had played out.

Jarred Reiling: And I think what's interesting about the Washington case is FDA's reaction to the dueling rulings, was to file a motion with the Washington court, and essentially say, what are we supposed to do here? And the judge said, you're supposed to follow my order, I don't care what happens.

Whitney Cloud: But Jarred, you raised an interesting point, because the court doesn't really have to worry about its ramifications, but states that are willing to distribute Mifepristone and wanting to distribute Mifepristone, and obviously these 17 states and the District of Columbia did, they were left in a quandary if Judge Kacsmaryk's decision had gone forward. Whereas a state like Texas or Idaho, or one of the many other states that have essentially banned abortion except for very limited exceptions, it's still going to be illegal under state law to distribute Mifepristone, within those state boundaries. But the real crux of Judge Kacsmaryk's decision is the distribution of Mifepristone in all states. So, there's quite a lot at stake before the Fifth Circuit and the Supreme Court in the next year.

Jarred Reiling: Without a doubt.

Bethany Hills: All right, and with that, I think we will wrap up. Thank you very much, Whitney, Katie, and Jarred for bringing your expertise to this discussion, helping us

think about the future impacts to life science innovators, and of course, their important interactions with FDA.