Conversations With...

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Federal Preemption in Pharmaceutical Product-Liability Litigation

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Introduction: The Food, Drug and Cosmetic Act grants the Food and Drug Administration plenary authority over prescription drug review, marketing approval, and post-marketing oversight. A pharmaceutical manufacturer must strictly comply with FDA's labeling requirements in order to market their product. FDA interprets that authority very broadly.

Whether the health warnings that FDA requires drug makers to include on product labels are adequate is a question that arises frequently in product-liability lawsuits filed under state law. Plaintiffs in such cases allege that the manufacturer's failure to warn of certain risks caused their injury. Such an argument beget a potential collision of authority: Can a judge, applying state law, require a new or different warning than that which FDA has required?

In such circumstances, pharmaceutical defendants may argue that federal law preempts the application of state-law warning mandates as a remedy in product-liability litigation. A 2008 U.S. Supreme Court decision, *Wyeth v. Levine*, set out some parameters for such a preemption defense. The Court has issued several drug preemption decisions since *Wyeth*, including a 2019 ruling that placed assessment of defendants' "impossibility preemption" arguments in the hands of judges.

In this WLF Conversations With, a group of attorneys who have considered federal preemption as trial counsel, senior federal officials, in-house counsel, and judicial clerks join us to discuss the latest federal-court jurisprudence on such key questions as what constitutes "newly acquired information" and whether judges can make factual determinations when evaluating preemption claims.

Let's start off with a brief overview of the U.S. Supreme Court's preemption jurisprudence in the area of state-law product-liability claims where the plaintiff alleges that a prescription drug manufacturer failed to warn of a side effect or other risk. Dan Troy, what did the Court decide in *Wyeth* on the question of federal preemption?

Daniel Troy: In *Wyeth*, the claim was that Wyeth had failed to update its warning on a product called Phenergan. The Supreme Court held that the plaintiff's claim was not preempted and could go forward because Wyeth had the power under the Food and Drug Administration's "Changes Being Effected" regulation to change the warning unilaterally.

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There had been some engagement between FDA and Wyeth, but the Court found that there wasn't sufficient engagement for the state-law claim of failure to warn to be preempted. It was a 6-3 decision with Justices Breyer and Thomas writing important concurrences.

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The Court has addressed preemption in the drug labeling context three times since *Wyeth*. Dan, what did the *Mensing* and *Bartlett* decisions add to the law?

Troy: Those were polar opposite cases from *Wyeth*. In *PLIVA v. Mensing*, Justice Thomas wrote for a five-justice majority that because of the way the Hatch-Waxman Act works, the generic company had no ability to change the labeling. And as a result, the state-law claim, which said that the generic was obligated to change the labeling, was indeed preempted. Justice Thomas's authorship of the majority opinion was notable because he has very unique views on preemption.

In the second case, *Mutual Pharmaceutical v. Bartlett*, the U.S. Court of Appeals for the First Circuit basically concluded that the Supreme Court got it wrong in *Mensing* and the appellate court was determined to find a way around it. The First Circuit reasoned that instead of being subjected to a product-liability lawsuit, the pharmaceutical company could always stop marketing the generic drug.

The Supreme Court reversed the First Circuit in another 5-4 decision, with Justice Alito writing for the majority and Justices Kagan, Sotomayor, Breyer, and Ginsburg dissenting. The majority explained that the Court meant what it said in *Mensing*—there really is preemption of failure-to-warn claims for generic drugs. And you can't require a company to avoid the impossibility of complying with both federal and state law by removing the drug from the market. In almost every area of preemption, people could always stop economic activity. The Court said that just goes too far.

Finally, a little over two years ago, the Court decided the third post-*Wyeth* decision, *Merck Sharp & Dohme v. Albrecht*. How does that decision fit into our discussion?

Troy: So that case goes back to the branded side. And what's significant about *Albrecht* is that the Court says that it is a matter of law for the judge to decide whether or not the FDA's engagement with the product was sufficient to support preemption of the state failure-to-warn claim. The vote was 9-0, but Justice Thomas basically said, well, when this is remanded, there shouldn't be preemption. Three concurring justices, Chief Justice Roberts and Justices Alito and Kavanaugh disagreed and wrote that on remand, the state-law claim should be preempted.

But what's most important about *Albrecht* is its clearly stating that preemption is a matter of law, not a factual determination for the jury. Defendants could thus raise the preemption defense perhaps at the motion-to-dismiss stage, certainly at the summary-judgment stage, and in some cases during post-trial motions. These incredibly complicated questions are no longer in the hands of juries. The justices made clear in *Albrecht* that even if in the course of the preemption determination the judge must engage with so-called brute facts about what happened vis-a-vis the FDA and the company, that would be an acceptable determination.

In *Albrecht*, the Solicitor General filed an *amicus* brief in support of the Petitioner. Dan Feith, why was that significant and what did the government argue?

Daniel Feith: The Solicitor General's brief in *Albrecht* was significant in a couple respects. The brief embraced quite a broad view of preemption. That view was much closer to the position adopted in Justice Alito's concurrence than to the majority's narrower, but still pro-preemption view. The government made two basic arguments. First, the question of whether the FDA would disapprove of a proposed warning is a question of law for courts to resolve rather than a question of fact for the jury.

Second, in the context of that particular case, the FDA's complete response letter embodied a determination that there was insufficient causal evidence to warrant strengthening the label. And in making that argument, the government drew an inference from FDA inaction on the theory that the FDA has a statutory duty under the 2007 Food and Drug Administration Amendments Act to strengthen a label when it believes there is a basis to do so.

The second significant aspect of the SG's brief was the point it made about the danger of over-warning. The government explained that in determining which warnings to include, the FDA tries to strike a balance and avoid including too many warnings on the label. The government identified two problems with over-warning. First, over-warning dilutes the most important warnings. Second, over-warning deters appropriate and beneficial uses of the drugs. This is representative of the delicate cost-benefit balance that the FDA has to strike with drug approvals and why preemption is such an important doctrine in this space.

Let's talk about how *Albrecht* has affected drug product-liability trial defense work, which is Robert's area of expertise. What are you now doing differently in cases where preemption is a defense?

Robert Johnston: In *Albrecht*, the Court began to elucidate what is "clear evidence of FDA action." Does that standard require an actual, formal statement by the FDA saying you can't make this label change, or is there something less that is sufficient? The commitment of that core, root factual question to the judge has also opened up the gates for defendants to cite, for instance, to FDA rejection of a citizen petition requesting the very labeling change that the plaintiff claims is unlawfully missing as "clear evidence."

And on the question of whether the types of newly acquired evidence alleged in a failure-to-warn complaint are adequate to trigger a defendant's use of the changes being effected regulation, some judges have taken *Albrecht* to mean that the court can make that determination as early as the motion-to-dismiss stage. That's providing defendants a very early opportunity to address preemption based on their inability to utilize the changes being effected rule. In a 2019 decision in *Gibbons v. Bristol-Myers Squibb Co.*, the Second Circuit affirmed a series of multi-district litigation (MDL) court orders that dismissed failure-to-warn claims involving the drug Eliquis as preempted by federal law. The Second Circuit conducted a very thorough

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evaluation of the supposed newly acquired information that allegedly compelled an additional warning, finding it lacking.

Other judges, however, may be more skeptical than the Second Circuit panel in *Gibbons* about making a preemption decision at the motion-to-dismiss stage because judges generally assume that you can't talk about facts at that stage. And frankly, the federal civil-procedure rules don't really provide a mechanism for fact finding and fact presentation at the motion-to-dismiss stage. So that's something that we're still going to have to work on, but it's an interesting opportunity that's out there.

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Now that we've laid the groundwork on the applicable judicial precedents on preemption in failure-to-warn drug suits, we're going to use two recent court decisions to examine how federal judges are addressing the preemption defense as a matter of law, with a particular focus on the "changes being effected" rule. The first is a January 6, 2021 Fourth Circuit decision, *Knight v. Boehringer Ingelheim*. There, the key question was whether the manufacturer had newly acquired information.

Dan Feith, what did the trial court decide on that question?

Feith: *Knight* involved claims that drug manufacturer Boehringer Ingelheim failed to adequately warn of the risk of uncontrollable bleeding associated with a blood-thinning medication, Pradaxa. And as you noted, the dispute in *Knight* was whether Boehringer had newly acquired information, namely that there was an optimal blood concentration for Pradaxa that called for a strengthened warning under the changes being effected regulation. Pradaxa had been approved without any optimal blood concentration range or blood monitoring requirement, which was viewed as a selling point in comparison to its main competitor.

The *Knight* plaintiffs argued that the newly acquired information Boehringer was aware of arose from the preliminary results of the so-called Reilly Paper. The Reilly Paper was a post-approval review of the results of one of the clinical studies that Boehringer had relied on for production approval. The study's preliminary results pointed to there being an optimal blood concentration range, even though the final published Reilly Paper ultimately concluded that there was no such optimal range. The federal district court agreed with the plaintiffs and held that that Boehringer had newly acquired information in the form of, first, the preliminary results themselves of the paper and, second, from emails among Boehringer employees discussing those results.

On appeal the Fourth Circuit reversed. Why did the court find that the Reilly Paper's preliminary findings were not newly acquired information?

Feith: The Fourth Circuit's decision in this case really demonstrates the value of having courts police what constitutes newly acquired information. The decision shows that plaintiffs have a real threshold to overcome before you even get to the

question that Robert was discussing about whether the FDA would have disapproved the warning, or whether a manufacturer could act unilaterally. In *Knight*, the Fourth Circuit gave two reasons that the Reilly Paper's preliminary findings were not newly acquired information. First, it emphasized that the preliminary results were tentative and subject to further study. The court noted that at the time the initial drafts were circulated, Dr. Reilly, the lead author on the paper, had said that he wanted to see where the paper took him. And in fact, Dr. Reilly then proceeded to spend an additional couple of years working on the paper.

The Fourth Circuit also stressed that the paper ultimately reached a different conclusion, and that different conclusion was accepted by the scientific and regulatory community. The paper was peer reviewed, published, and submitted to the FDA. The FDA then relied on the paper to continue Pradaxa approval without any blood monitoring requirement. Importantly, in deciding not to treat preliminary results as newly acquired information, the Fourth Circuit recognized the policy interest of improving the scientific process by allowing the open dialogue and exchange of ideas and hypotheses. That policy interest is akin to the deliberative-process privilege in federal agencies. The Fourth Circuit also recognized the risk of over-warning that we talked about earlier. If the threshold for newly acquired information were set too low, drug manufacturers would have an incentive to flood FDA with unnecessary information and to add unnecessary warnings to label.

How does *Knight* compare to decision in other circuits on the question of newly acquired information?

Feith: *Knight* is broadly consistent with how other courts have viewed the identification of newly acquired information as a threshold requirement if plaintiffs wish to avoid preemption of failure-to-warn claims. The First Circuit in *In re Celexa & Lexapro Marketing and Sales Practice Litigation* found the plaintiffs' failure-to-warn claims preempted because the complaint identified only information that had been before FDA at the time of approval. The Third Circuit's *In re Avandia Marketing, Sales, and Product Liability Litigation* decision somewhat implicitly recognizes this rule. The *In re Incretin-Based Therapies Products Liability Litigation* that we'll discuss in a bit similarly distinguishes between preliminary and final assessments and recognizes that only the latter can qualify as newly acquired information. I think *Knight* really does represent a step forward. It is by far the most in-depth treatment of the metes and bounds of newly acquired information.

Dan Troy, as someone who's worked in the pharmaceutical industry, I can imagine that you were pleased to see the Fourth Circuit acknowledge the risks of chilling scientific discussion and interaction at the preliminary stage?

Troy: I certainly was. Looking at cases like *Knight* from a broader perspective, let me suggest a way that I think about preemption which is not exactly the way most courts do. For me, it's a useful sort of heuristic and way of looking at these cases and kind of harmonizing them. And that is in the language of the *Chevron* doctrine: has the FDA directly spoken to the precise question at issue? Consider the outcome of cases like *In re Incretin*, where the FDA has directly spoken to the precise question

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at issue, or *Bartlett*, where the regulations directly spoke to the precise question at issue. Then I think the case for preemption is really strong. If you can't make the case that the FDA has really been forced to think about this one way or the other, whether it's a response to a citizen petition or it's a response to a labeling request, then your preemption defense might not succeed.

"I look at these preemption cases using the language of the *Chevron* doctrine: has the FDA directly spoken to the precise question at issue? Consider the outcome of cases like *In re Incretin*, where the FDA has directly spoken to the precise question at issue, or *Bartlett*, where the regulations directly spoke to the precise question at issue. Then I think the case for preemption is really strong."

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In *Knight*, the Fourth Circuit reasoned "the record does not demonstrate that Dr. Riley's emails or the draft papers, preliminary assessments of an optimal Pradaxa blood concentration level, reflected a revelation of risks of a different type or greater severity or frequency." So the point is the labeling of Pradaxa had directly spoken to the precise question at issue of blood concentration levels, and even the preliminary analysis didn't really upend and change it. And certainly the later analysis just kind of confirmed what FDA had already precisely spoken to on the labeling. And so that's why I think the Fourth Circuit came to the right conclusion. And I think we'll see again, as we talk about the next case, that where the FDA has really engaged the scientific question in whatever way, shape or form, then I think you have a much better case for preemption.

Thank you, Dan. The next case we'll discuss, as both Dan Troy and Dan Feith alluded to, is the March 9, 2021 *In re Incretin* decision from Southern District of California. There, the court granted four drug companies' joint motion for summary judgment in an MDL bellwether trial. Whether the companies possessed newly acquired information was also a threshold issue in this case.

Robert, on the newly-acquired-information question, the court's meticulously reasoned opinion focused on the type and quality of scientific evidence plaintiffs advanced, and the court was clearly unimpressed with what it saw, correct?

Johnston: That's correct. I think *In re Incretin* in many ways is simply the latest of a series of cases where judges are willing to undertake the hard work of looking at those brute facts in evaluating plaintiff's claims, even at the preliminary motions stage. The plaintiffs alleged that the pharmaceutical products at issue increased the risk of pancreatic cancer. There were several things that the plaintiffs pointed to as newly acquired evidence. One was the commissioning of an epidemiological inquiry by Health Canada. The plaintiffs argued that a foreign regulatory body's decision to start an inquiry into the epidemiology of pancreatic cancer in these treated patients somehow constituted new evidence that required a label change. The plaintiffs also relied upon several studies, none of which focused on the end point at issue, and instead focused on things like the rates of pancreatic cancer. The court concluded that none of those studies, properly interpreted, demonstrated a change in the frequency or severity of this adverse event, which had already been recognized in submissions to the FDA, tracking Dan Troy's point that where you've had a conversation with the FDA about the event at issue, and the FDA took no action, you should win on preemption.

That's a much better place to be than a world where you haven't had a conversation with the FDA. I think though that some of these cases suggest that that interaction with the FDA could be as simple as a phone call in some instances. Now, that may

be pushing it. A phone call with the FDA, standing alone, might not be enough. But what defendants don't have to have is some detailed medical analysis from the FDA evaluating the side effect. If the folks at the FDA have said, "we understand that risk is present, we think your labeling is adequate, notwithstanding that risk," that should be enough interaction for a court to dismiss on preemption grounds.

What's particularly fascinating about *In re Incretin* is that it's in the Southern District of California, which means that we're in Ninth Circuit world, not generally the most hospitable place for a federal preemption arguments. For that reason, it's a little bit surprising that a California federal court is one of the early adopters of scrutinizing the brute facts of a preemption defense in pre-trial motions. I think it's suggestive that the logic of this approach is hard to get around. And I think that's good.

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The plaintiff argued that FDA inaction can never support a preemption finding. What was the court's response to that?

Johnston: I think what the court said about that is if the FDA knows about a risk and knows the data related to that risk, the fact that you could interpret the study differently, or you can hypothesize a risk of a different magnitude or severity, is not going to move the ball on newly acquired information, where the there's a baseline showing that there was an interaction with the FDA about the issue at some level.

Troy: So I agree with everything you said Robert, and it is worth stressing that the FDA's engagement with this question of pancreatic cancer in *In re Incretin* was far more than a phone call. To quote the case, "as discussed above the FDA, through its own evaluation and armed with information from Defendants and other sources, considered the specific issue raised by Plaintiffs in this case: the pancreatic safety of incretin mimetics. At no point in its years-long monitoring of these drugs did the FDA require Defendants or any other manufacturer of incretin-based therapies to add a pancreatic warning to its label. Quite the contrary, the FDA has published its findings regarding the pancreatic safety of incretin mimetics, commented on the adequacy of the drug labeling, and maintained its position that scientific evidence of a causal association between incretin-based therapies and pancreatic cancer is indeterminate." I mean, the FDA's engagement on this question was actually over, over and over, and over again.

Yes, it's inaction, but it's a curious form of inaction because they are all over this question, right? Including publishing a very unusual paper that doesn't have the normal FDA disclaimer that these are only the views of the authors. I mean, it really seemed to purport to be a scientific analysis on behalf of the FDA, notwithstanding its "podium policy." To me, the defendants in *In re Incretin* have a very, very strong case. What to me will be interesting is if on appeal the Ninth Circuit reverses the Southern District, you've got a great Supreme Court case.

Feith: I agree with that. The *In re Incretin* decision is extremely interesting because it offers insights into how courts are thinking about a number of the legal questions that were left open from *Albrecht*, and as Dan and Robert have said, it answers almost all of them in a staunchly pro-preemption manner. For instance, after *Wyeth* and *Albrecht*, it was unclear whether, to establish an impossibility defense,

manufacturers must have actually proposed a labeling change that the FDA actually rejected. *In re Incretin* suggests the answer is actually no, at least, for instance, where the FDA published studies or was responsive to a citizen petitions. Some amount of clear evidence that the FDA was being fully informed and disapproved even if the manufacturer didn't tee up the issue to the agency directly, could be enough for a finding of preemption.

There has also been an open question about what agency actions suffice to establish disapproval—does there need to be final agency action carrying the force of law or may other types of agency actions suffice. And again, *In re Incretin* takes the broader view by, for example, relying on the FDA's published study. That is an action that comes up short of carrying the force of law, and yet the court found that to be sufficient evidence.

Johnston: Plaintiffs in failure-to-warn cases against pharmaceutical companies will portray anything short of final agency action as agency inaction. And as both Dan Troy and Dan Feith observed, the *In re Incretin* court did a very thorough job of looking factually at the companies' interactions with the FDA and recognizing that after the FDA failed to take action after becoming fully informed about a possible product risk, FDA acted by not acting. I think that's a fascinating way of looking at the court's decision.

It's clear from *Knight* and *In re Incretin* that there is room somewhere between final agency action and FDA ignorance that can still support preemption.

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