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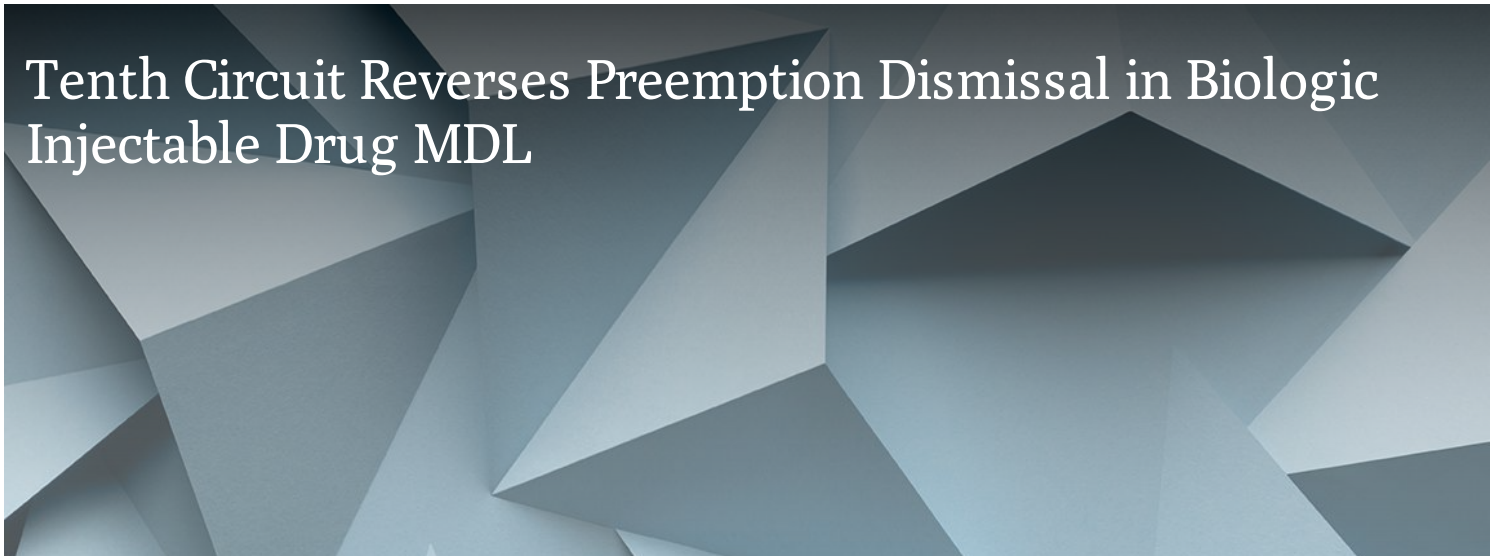
BLOG

Tenth Circuit Reverses Preemption Dismissal in Biologic Injectable Drug MDL



AUGUST 18, 2020

The doctrines of implied preemption and agency deference continue to develop with the Tenth Circuit's recent decision in *In re MDL 2700 Genentech Herceptin (Trastuzumab) Marketing and Sales Practice Litigation*. The decision is notable because the Tenth Circuit not only reversed the district court's holding that the plaintiffs' claims were preempted, but in arriving at this conclusion, the Tenth Circuit also expressly declined to defer to the FDA on whether the medication at issue was a liquid or solid for regulatory and labeling purposes.

Background

Genentech, Inc. manufactures the biologic product Herceptin, a prescription drug used to treat breast cancer. As a biologic drug, Herceptin is produced from a living organism: the production process includes harvesting the living cells, forming them into a protein solution, freezing the solution for shipping, thawing the solution once delivered, and eventually forming it into various freeze-dried "cakes" that contain solid protein in a procedure called lyophilization. *In re MDL 2700 Genentech Herceptin (Trastuzumab) Mktg. & Sales Practice Litig.*, 960 F.3d 1210, 1216-17 (10th Cir. 2020). These cakes are placed into vials for distribution. *Id.* Before being injected into a patient, the "cakes" are combined with sterile water from vials that accompany the protein vials. *See id.* Lyophilization has been increasingly used in the pharmaceutical industry because of its ability to improve product stability.

The FDA began receiving complaints about Herceptin in 2014 from cancer treatment providers who claimed that they were unable to withdraw the advertised amount of Herceptin from the vials. *In re Genentech, Inc.*, 367 F. Supp. 3d 1274, 1281 (N.D. Okla. 2019). In 2016, the cases were consolidated into an MDL to adjudicate breach of warranty and unjust enrichment claims alleging that Genentech failed to include the amount of the active ingredient that was advertised on the federally approved label: 440 mg at a concentration of 21 mg/mL. *Id.* at 1277.

The FDA's labeling requirements are slightly different depending on whether the medication is a solid or liquid. For instance, the label for *solid* drugs sold in vials must contain the accurate net weight of ingredients, *but reasonable variations are permitted*. *Id.* at 1285-86; 21 C.F.R. § 201.51(g). By contrast, for liquid drugs, the label must state "the *minimum* quantity" and reasonable lesser variations are not expressly permitted. 21 C.F.R. § 201.51(g) (emphasis added). In other words, the regulations allow for reasonable variations for solid drugs based on the unavoidable loss

or gain of moisture during manufacturing and distribution, but liquid drugs must contain the minimum stated quantity of the ingredient.

The FDA had treated Herceptin as a solid (allowing for reasonable variations). *Id.* at 1286.

The District Court's Decision

In March 2019, the District Court for the Northern District of Oklahoma granted summary judgment in favor of Genentech finding that the plaintiffs' claims were barred by the doctrines of obstacle and impossibility preemption. *In re Genentech, Inc.*, 367 F. Supp. 3d 1274, 1290 (N.D. Okla. 2019).

Obstacle Preemption. Obstacle preemption applies when state laws serve as an "obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Wyeth v. Levine*, 555 U.S. 555, 563-64 (2009) (quoting *Hines v. Davidowitz,* 312 U.S. 52, 67 (1941)). Here, the court held that the plaintiffs' claims regarding the label served as an obstacle to the FDA's "reasonable variation" allowance. *In re Genentech, Inc.*, 367 F. Supp. 3d at 1284-88. The court rejected the plaintiffs' argument that Herceptin is actually a liquid drug, finding that the FDA has always treated Herceptin as a solid drug, and thus permitted reasonable variations in net weight. *Id.*

Impossibility Preemption. The court also held that the plaintiffs' claims were barred by impossibility preemption. *Id.* at 1288-89. Impossibility preemption applies when it would be "impossible for a private party to comply with both state and federal requirements." *Id.* at 1282 (quoting *In re Universal Service Fund Telephone Billing Practice Litig.*, 619 F.3d 1188, 1196 (10th Cir. 2010)). Though the plaintiffs argued that Genentech could comply with their requests based on state law by altering either the manufacturing process or the product label, the court found that these changes would require prior FDA approval to change its manufacturing process or label information, and thus, were barred by impossibility preemption. *Id.* at 1288-89.

Finally, the court rejected the plaintiffs' suggestion that Genentech could comply with state law simply by continuing to sell only those vials that met the 440 mg concentration requirement. *Id.* at 1289-90. Reasoning that the Supreme Court had explicitly denied this "stop-selling" argument in *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013), the district court held that Genentech could not be forced to stop sales of drugs that complied with FDA regulations. *Id.* at 1290.

The Tenth Circuit's Reversal

On May 29, 2020, the Tenth Circuit reversed. *In re MDL 2700 Genentech Herceptin (Trastuzumab) Mktg. & Sales Practice Litig.*, 960 F.3d 1210 (10th Cir. 2020). The Tenth Circuit first addressed obstacle preemption. *Id.* at 1229-30. The Tenth Circuit agreed with the plaintiffs that nothing in the FDA regulations required the agency to monitor Genentech's distribution practices and confirm that the amount of Herceptin in each vial complied with its product label. *Id.* Rather, "the FDA establishes general labeling standards, but does not appear to routinely police manufacturers afterwards to ensure that they are fully complying with those standards." *Id.* at 1230-31. The court reasoned, therefore, that this "leaves room for states to impose their own requirements, so long as those requirements do not conflict with the federal regulatory scheme." *Id.* at 1231.

Accordingly, the court turned to the applicable FDA regulations to determine whether such a conflict exists and noted that "[b]ecause § 201.51(g)'s labeling requirements differ for 'liquid drug[s]' and 'solid drug[s],'" it must determine whether Herceptin is a liquid or solid drug as part of the preemption analysis. *Id.* at 1232. The court found that because Herceptin is administered as a liquid drug in vials intended for injection, it is subject to the liquid drug requirement that the label "express the minimum quantity" of the drug in each vial. *Id.* at 1234. Thus, the court held that the federal regulation required the vials to contain at least 440 mg of the active ingredient, which was consistent with the state law standards the plaintiffs sought to invoke in the case. *Id.* Consequently, the court held that obstacle preemption did not apply. *Id.*

The court then turned to impossibility preemption, and noted that Genentech's impossibility preemption arguments hinged on the notion that Herceptin is a solid drug and "the product label for Herceptin merely had to 'express the

accurate net weight' of the product" such that the contents could vary. *Id.* at 1235. The court reiterated that it considers Herceptin a liquid drug such that the label must express the *minimum* quantity of the active ingredient. *Id.* (emphasis added).

But this still left the question of whether it would have been impossible to comply with this requirement without receiving FDA preapproval. *Id.* at 1235-36. The Tenth Circuit concluded it was not. The court explained that the majority of Herceptin batches after 2009 contained less of the active ingredient advertised on the label, but that this was not a problem prior to that time. *Id.* at 1237-38. Thus, the court noted that this "suggests that Genentech, as it continued to manufacture Herceptin, obtained and exercised a high degree of control over its manufacturing process, and, in turn, may have knowingly targeted" the lower amount of active ingredient. *Id.* at 1238. All Genentech needed to do to comply with this standard, therefore, was return to its historical manufacturing practice. *Id.* at 1239.

Importantly, the court noted that only state law claims that call for "major changes" under the FDA regulations typically "give rise to impossibility pre-emption." *Id.* at 1236. While this observation did not help Genentech here, the court's statement is notable because it further solidifies the view that major changes to a label do, in fact, give rise to preemption. In affirming this principle, the Tenth Circuit has joined a growing body of courts that likewise recognize this concept. *See, e.g.*, *Yates v. Ortho-McNeil-Janssen Pharmaceuticals, Inc.*, 808 F.3d 281, 298 (6th Cir. 2015) ("Yates's post-approval design defect claim is clearly preempted by federal law. FDA regulations provide that once a drug, whether generic or brand-name, is approved, the manufacturer is prohibited from making any major changes to the 'qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application.'"); *Gustavsen v. Alcon Laboratories, Inc.*, 903 F.3d 1, 14 (1st Cir. 2018) ("[W]e therefore conclude that changing the product bottle so as to dispense a different amount of prescription eye solution is a 'major change' under 21 C.F.R. § 314.70(b). That conclusion, in turn, means that plaintiffs' attempt to use state law to require such a change is preempted.").

Role of FDA Deference in Determining Preemption

Notably, the Tenth Circuit declined to defer to the FDA in determining that Herceptin is a liquid drug. The court noted that it need not provide agency deference when a regulation is unambiguous. *In re MDL 2700 Genentech Herceptin*, 960 F.3d at 1232 (citing *Kisor v. Wilkie*, 139 S. Ct. 2400 (2019)).

Here, the Tenth Circuit reasoned that the regulatory language was clear, and thus deference was unnecessary. *Id.* at 1233-34. Specifically, the Tenth Circuit found that under the regulations, it is the form of administration that controls, and Herceptin had always been intended for injection into patients. *Id.* at 1233. So even though the FDA had previously treated Herceptin as a solid drug in practice (though the Tenth Circuit found no evidence of this), the court nevertheless concluded it was a liquid drug due to its ultimate injectable form of administration. *Id.* at 1234.

This is particularly significant for manufacturers of injectable products because the Tenth Circuit's reasoning suggests that *all* injectables are liquid drugs subject to liquid drug regulatory requirements. This approach ignores the regulation's language that solid drugs may be contained in ampules or vials. Indeed, the FDA explicitly recognizes that injectable products may be solid drugs. *See* FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics at 23 ("Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension."). The Tenth Circuit's decision has effectively expanded the reach of the liquid drug minimum quantity condition beyond what even the FDA has traditionally required.

Manufacturers Should Take Note, Particularly Those of Injectable and Biologic Products

Ultimately, the Tenth Circuit's decision in *In re MDL 2700 Genentech Herceptin* creates more uncertainty for drug manufacturers navigating a complex regulatory scheme. One positive aspect of the court's decision is that it has confirmed that the Tenth Circuit views "major changes" to drug labels as events precipitating impossibility preemption. But perhaps more significant is the court's narrowing of deference provided to the FDA in determining

how drug products are classified. Manufacturers of lyophilized biologic or biosimilar injectable products, in particular, should be aware that the classification of their drugs as either solids or liquids may not end with the FDA's assessment, and they may be subject to different regulatory requirements as a result.

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