Case No. 19-5035

IN THE UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

IN RE: MDL 2700 GENENTECH HERCEPTIN (TRASTUZUMAB) MARKETING AND SALES PRACTICES LITIGATION.

TULSA CANCER INSTITUTE, PLLC, an Oklahoma Professional Limited Liability Company, n/k/a Oklahoma Cancer Specialists Management Company, LLC; OKLAHOMA ONCOLOGY & HEMATOLOGY, INC., an Oklahoma Corporation, d/b/a Cancer Care Associates; STATE OF OKLAHOMA EX REL. BOARD OF REGENTS FOR THE STATE OF OKLAHOMA; FLORIDA CANCER SPECIALISTS, P.L., a Florida Professional Limited Liability Company; HEMATOLOGY-ONCOLOGY ASSOCIATES OF CENTRAL NEW YORK, P.C., a New York Professional Corporation; VIRGINIA CANCER INSTITUTE, INC., a Virginia Commonwealth Professional Corporation; TENNESSEE ONCOLOGY, PLLC, a Tennessee Professional Limited Liability Corporation; NORTH SHORE HEMATOLOGY-ONCOLOGY ASSOCIATES, P.C., a New York Professional Corporation; TEXAS ONCOLOGY, P.A., a Texas Professional Association; CANCER CARE NETWORK OF SOUTH TEXAS, P.A.; VIRGINIA ONCOLOGY ASSOCIATES, P.C.; MINNESOTA ONCOLOGY HEMATOLOGY, P.A.; COMANCHE COUNTY MEMORIAL HOSPITAL, on behalf of itself and all others similarly situated; NORTHWEST CANCER SPECIALISTS, P.C., an Oregon Professional Corporation, d/b/a Compass Oncology; ONCOLOGY AND HEMATOLOGY ASSOCIATES OF SOUTHWEST VIRGINIA, INC., d/b/a Blue Ridge Cancer Care; SHENANDOAH ONCOLOGY, PC; ONCOLOGY-HEMATOLOGY ASSOCIATES OF CENTRAL ILLINOIS P.C.,

Plaintiffs-Appellants,

v.

GENENTECH, INC., a California Corporation,

Defendant-Appellee,

and

ROCHE HOLDING AG; ROCHE HOLDING LTD.; ROCHE HOLDINGS, INC.,

Defendants.

Appeal from a Decision of the United States District Court for the Northern District of Oklahoma,
Case Nos. 4:16-MD-02700-TCK-JFJ, 4:15-CV-00157-TCK-JFJ, 4:16-CV-00202-TCK-JFJ
4:16-CV-00203-TCK-JFJ, 4:16-CV-00204-TCK-JFJ, 4:16-CV-00206-TCK-JFJ, 4:16-CV-00205-TCK-JFJ, 4:16-CV-00207-TCK-JFJ, 4:16-CV-00210-TCK-JFJ, 4:16-CV-00221-TCK-JFJ, 4:16-CV-00347-TCK-JFJ, 4:16-CV-00359-TCK-JFJ, 4:16-CV-00419-TCK-JFJ, 4:16-CV-00424-TCK-JFJ, 4:17-CV-00394-TCK-JFJ
Honorable Terence C. Kern, U.S. District Judge

APPELLANTS' OPENING BRIEF (REDACTED)

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Fed. R. App. P. 26.1 and 28, each of the following Plaintiffs/Appellants states that it is a non-governmental entity.[1] Each also states that it does not have a parent corporation and that no publicly-held corporation owns 10% or more of the party's stock.

Cancer Care Network of South Texas, P.A.

Comanche County Memorial Hospital

Florida Cancer Specialists, P.L.

Hematology-Oncology Associates of Central New York, P.C.

Minnesota Oncology Hematology, P.A.

North Shore Hematology-Oncology Associates, P.C.

Northwest Cancer Specialists, P.C.

Oklahoma Oncology & Hematology, Inc.

Oncology and Hematology Associates of Southwest Virginia, Inc.

Oncology-Hematology Associates of Central Illinois, P.C.

Shenandoah Oncology, PC

Tennessee Oncology, PLLC

Texas Oncology, P.A.

[1] Plaintiff/Appellant State of Oklahoma ex rel. Board of Regents for the State of Oklahoma is a governmental entity.

Tulsa Cancer Institute, PLLC (now known as Oklahoma Cancer Specialists Management Company, LLC)

Virginia Cancer Institute Inc.

Virginia Oncology Associates, P.C.

Dated: July 31, 2019

/s/ David L. Bryant
David L. Bryant, OBA No. 1262

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GLOSSARY OF TERMS

1906 Act – Pure Food and Drugs Act of 1906

Active ingredient – any component of a drug product intended to furnish pharmacological activity

Biologics – drugs that are produced from living organisms

BLA – Biologic License Application – application submitted by manufacturer to FDA to seek permission to distribute biologic drug

BWFI – Bacteriostatic Water for Injection

CBE – Changes Being Effected in 30 days; document notifying FDA that a drug manufacturer plans to make changes to its manufacturing processes or labeling in 30 days. Manufacturers need not wait to distribute drugs made using the change.

Draft Guidance – FDA Draft Guidance for Industry, *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (March 2014)

Drug product – a medication in the form in which it is marketed, including active and inactive ingredients

Drug substance – the active ingredient in a drug

FDA – U.S. Food and Drug Administration

FDCA - Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq*.

Final Guidance – FDA Guidance for Industry, *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015)

FPLA – Fair Packaging and Labeling Act, 15 U.S.C. § 1451, *et seq.*

Herceptin Solution – solution produced when Herceptin drug product is reconstituted according to package directions to be administered to patient

IRCA – Immigration Reform and Control Act

Lyophilized – freeze-dried

PAS – Prior Approval Supplement, a document submitted to FDA to obtain FDA's approval for major changes to prescription drug manufacturing; must be approved by FDA prior to distribution of any drug manufactured using the change

Specifications – criteria to be used in determining whether a lot of a drug is sufficiently similar to the drug product samples approved by FDA.

Strength – the amount of the active ingredient in a drug

Trastuzumab – the active ingredient in Herceptin

Q&A Memo – memo prepared by Genentech in 2014 to help Genentech employees answer questions from healthcare providers regarding why they could not obtain the labeled amount from Herceptin 440 mg vials

USP – U.S. Pharmacopeia, a compendium of drug information

PRIOR OR RELATED APPEALS

There are no prior or related appeals pending in this Court.

JURISDICTIONAL STATEMENT

The district court had jurisdiction over this matter under 28 U.S.C. § 1332 and the Class Action Fairness Act of 2005. On March 20, 2019, the district court granted summary judgment in favor of Genentech. Appellants' Appendix ("AA") 1315. The same day, the court entered final judgment for Genentech. AA1338. Plaintiffs filed a notice of appeal under Federal Rule of Appellate Procedure 4(a)(1)(A). AA1344. This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

1. The district court failed to identify any federal purpose to which Plaintiffs' state-law claims impose an obstacle, and no such federal purpose exists. Did the court err in concluding that obstacle preemption bars Plaintiffs' state-law claims?

2. For years, Genentech's Herceptin manufacturing process consistently produced product vials that met the label claim. Then, suddenly, that changed, without any FDA-approved change in Genentech's manufacturing process. Genentech presented no undisputed evidence establishing that it would be impossible for Genentech to meet its Herceptin label claim without making manufacturing process changes of a kind that would require prior FDA approval. Did the court err in applying impossibility preemption?

3. The district court completely failed to analyze Plaintiffs' claim that Genentech misstated the concentration of reconstituted Herceptin Solution, yet summarily ruled this claim is barred by obstacle and impossibility preemption. Did the court err?

STATEMENT OF THE CASE AND FACTS

I. Introduction

Genentech manufactures and distributes the cancer drug Herceptin. From 1998 to 2017, Genentech sold Herceptin in the United States in multi-dose vials. The Herceptin packaging stated that each package contained 440 mg of Herceptin's active ingredient, called trastuzumab. But starting in 2009, more than 80% of the Herceptin vials Genentech sold contained less than the labeled amount of the drug.

Plaintiffs are healthcare providers who purchased Herceptin to administer to their cancer patients. When they realized they were unable to obtain the warranted amount of Herceptin from the multi-dose vials, they brought state-law claims against Genentech based on the underfill. Genentech admitted that it systematically underfilled Herceptin vials but moved for summary judgment, arguing that federal law allowed it to provide less than the labeled amount of medication despite its promises and therefore preempted the state-law claims. The district court agreed, holding that the state-law claims were preempted under both obstacle and impossibility preemption.

II. Statutory background

A. Congress has long protected consumers from adulterated and misbranded prescription drugs.

For over a century, Congress has protected consumers from dangerous prescription drugs by regulating the manufacturing and distribution of those drugs. In the wake of public outcry following Upton Sinclair's landmark exposé in *The Jungle*, Congress passed the Pure Food and Drugs Act of 1906 ("**1906 Act**"), which prohibited the manufacture or interstate shipment of adulterated or misbranded food and drugs.[2]

This first legislative effort, however, had numerous shortcomings. After more than 100 people—including many children—died from taking a new, untested drug containing a chemical analogue to antifreeze,[3] an "increasing[] concern[] about unsafe drugs and fraudulent marketing" led Congress to replace the 1906 Act with the Federal Food, Drug, and Cosmetic Act ("**FDCA**"), 21 U.S.C. § 301 *et seq*. *Wyeth v. Levine*, 555 U.S. 555, 566 (2009). Like its predecessor, the FDCA "was designed primarily to protect consumers from dangerous products." *United States v. Sullivan*,

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[2] *Part I: The 1906 Food and Drugs Act and Its Enforcement*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/part-i-1906-food-and-drugs-act-and-its-enforcement (last updated Apr. 24, 2019).

[3] *Part II: 1938, Food, Drug, Cosmetic Act*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/part-ii-1938-food-drug-cosmetic-act (last updated Nov. 27, 2018).

332 U.S. 689, 696 (1948). It sought to "safeguard the consumer" by extending federal oversight to prescription drugs from the moment they were introduced into interstate commerce until they were delivered to the consumer. *Id.* The FDCA established the U.S. Food and Drug Administration ("**FDA**") to exercise this oversight. *See* 21 U.S.C. § 393(a).

B. Congress intended federal drug laws to supplement state law.

The history of federal drug regulation shows an intent by Congress to "supplement[]"—not replace—"the protection for consumers already provided by state regulation and common-law liability." *Wyeth*, 555 U.S. at 566; *see Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 498 (2013) ("[F]ederal drug law and state common-law liability have long been understood to operate in tandem to promote consumer safety.") (Sotomayor, J., dissenting).

In fact, the FDCA does not contain a private right of action for damages for consumers injured by prescription drugs. *See* 21 U.S.C. § 337(a) ("[A]ll . . . proceedings for the enforcement, or to restrain violations of [the FDCA] shall be by and in the name of the United States."). Although Congress considered adding such a provision, it declined to do so after testimony that a private "right of action was unnecessary because common-law claims were already available under state law." *Wyeth*, 555 U.S. at 574-75, 574 n.7. Thus, those seeking damages relating to prescription drugs may obtain relief only by bringing claims under state law. *See,*

e.g., id. at 558, 581 (affirming jury verdict awarding damages based on state-law claim that drug manufacturer failed to provide adequate warning about the risks of administering drug by IV-push method, resulting in amputation of the plaintiff's arm); *Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528, 532, 540 (6th Cir. 1993) (affirming jury verdict in favor of mother whose use of drug during pregnancy resulted in heart failure; drug manufacturer was strictly liable under state products liability law based on drug's defective design); *In re Epogen & Aranesp Off-Label Mktg. & Sales Practices Litig.*, 590 F. Supp. 2d 1282, 1290-91 (C.D. Cal. 2008) (permitting claims under state consumer fraud laws for deceptive advertising that allegedly caused consumers to pay millions of dollars for drugs prescribed for ineffective and unsafe off-label uses). Where, as in cases involving prescription drugs, Congress did not provide a federal remedy, the Supreme Court has cautioned against interpreting federal law to "remove all means of judicial recourse for those injured." *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984).

Congress's desire to ensure that state law effectively operates alongside the federal regulatory scheme is also reflected in the FDCA's express preemption language. In 1962, for instance, Congress added an express preemption provision that was intentionally narrow: It specified that "a provision of state law would only be invalidated upon a 'direct and positive conflict' with the FDCA." *Wyeth*, 555 U.S. at 567 (citing Drug Amendments of 1962, § 202, 76 Stat. 781, 793). Fifteen years

later, Congress expanded the scope of FDCA preemption, but only for state laws imposing requirements on medical devices that differed from the FDCA. *See* 21 U.S.C. § 360k(a). Congress ***did not*** add a similar provision for prescription drugs.

Indeed, through the years, although Congress has "enlarged the FDA's powers to protect the public health and assure the safety, effectiveness, and reliability of drugs," it has, at the same time, intentionally taken "care to preserve state law." *Wyeth*, 555 U.S. at 567 (internal quotation marks omitted); *see United States v. Dotterweich*, 320 U.S. 277, 282 (1943) ("Nothing is clearer than that the [FDCA] was designed to enlarge and stiffen the penal net and not to narrow and loosen it."). As the Senate Committee explained, the FDCA "'must not weaken the existing laws,' but on the contrary 'it must strengthen and extend that law's protection of the consumer.'" *Dotterweich*, 320 U.S. at 282 (quoting S. Rep. No. 75-152 at 1 (1937)).

C. The FDCA serves dual purposes of enforcement and regulation.

The FDCA protects the public from dangerous prescription drugs in two separate ways. First, it prohibits the sale and distribution of misbranded or adulterated drugs and authorizes the federal government to enforce that prohibition through criminal and civil penalties. Second, it creates a regulatory framework governing the manufacture and distribution of prescription drugs, including requiring that FDA review drugs before they enter the market to "ensure" they are "safe and effective for their intended use." Kathryn B. Armstrong & Jennifer A.

Staman, Cong. Research Serv., R43609, Enforcement of the Food, Drug, and Cosmetic Act: Select Legal Issues 4 (2018).

1. The FDCA makes it illegal to sell "misbranded" or "adulterated" drugs.

The FDCA explicitly prohibits drug manufacturers from selling "misbranded" or "adulterated" drugs through interstate commerce. 21 U.S.C. § 331(a). It lists a number of ways in which a drug may be misbranded. *Id*. § 352. Among these, the FDCA provides that a drug distributed in package form is misbranded if its label lacks "an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count." *Id.* § 352(b). The FDA may further define what constitutes misbranding under the FDCA by adopting regulations permitting "reasonable variations" in the quantity of package contents. *Id.*

Under this delegated authority, the FDA promulgated 21 C.F.R. § 201.51, which details how the "[d]eclaration of net quantity of contents" should be determined. Like its statutory counterpart, the regulation requires "an accurate statement of the quantity of contents" of a prescription drug package. *Id.* § 201.51(g). It provides that "[r]easonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized." *Id.*

Section 201.51(g) further provides that for a "liquid drug in ampules or vials" that is "intended for injection," the package should state "the minimum quantity" of

the drug in the package. *Id*. A package containing a "solid drug in ampules or vials" should state the "accurate net weight" of the drug. *Id.* Any "[v]ariations" in weight must "comply with the limitations provided in the U.S. Pharmacopeia" ("**USP**"), a compendium of drug information. *Id*.

The FDCA makes misbranding punishable by imprisonment for up to one year or a fine of $1000, or both. 21 U.S.C. § 333(a)(1). Upon a finding of an intent to defraud or mislead the consumer, the potential penalty for misbranding increases to imprisonment for up to three years or a fine of up to $10,000, or both. *Id.* § 333(a)(2).

2. FDA must approve new drugs before their distribution.

Congress also charged the FDA with "ensuring that prescription drugs are 'safe for use under the conditions prescribed, recommended, or suggested' in the drug's 'labeling.'" *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019) (quoting 21 U.S.C. § 355(d)). Before a manufacturer may introduce a new drug into interstate commerce, it must first file an application with FDA and obtain FDA's approval of the drug. *See* 21 U.S.C. § 355. This process applies to drugs that are produced from living organisms, known as "**biologics**."

When a manufacturer seeks to distribute a biologic, the FDA must first approve the company's Biologic License Application ("**BLA**"). 21 C.F.R. § 601.2. A BLA contains an extensive description of research, testing, and manufacturing information regarding the proposed product. AA1857. It also lists criteria—called

the product's "**specifications**"—to be used in determining whether a batch of the biologic is sufficiently similar to the drug product samples approved by FDA. *Id.* These specifications include criteria for determining whether the batch contains the FDA-approved amount of the active ingredient, referred to as the "**strength**" of the drug. *Id.*; *see* 21 C.F.R. § 211.165(a). If a batch of drug product does not meet the specifications, it cannot be distributed to the public and must be rejected. 21 C.F.R. § 211.165(f).

The manufacturer must also submit "specimens of the labeling proposed to be used" for the drug. 21 U.S.C. § 355(a); *see* 21 C.F.R. § 601.2(a). "The FDA is primarily concerned with ensuring that the label provides useful information to health care professionals." Office of Inspector Gen., Dep't of Health & Human Servs., FDA's Review Process for New Drug Applications 18 (2003).

III. Factual background

A. Genentech received FDA approval for Herceptin 440 mg.

Herceptin is a biologic drug made from **trastuzumab**, a human protein produced by cells from a Chinese hamster ovary cell line. AA1856. The trastuzumab is known as the "**drug substance**." *Id.* After the drug substance is harvested, it is frozen and shipped to a manufacturing facility, where it is placed into individual sterile vials. *Id.* The drug substance is lyophilized, or "freeze-dried," within the vial, creating the Herceptin "**drug product**." *Id.* If the Herceptin passes its compliance

testing, it is then distributed and ultimately sold to healthcare providers for administration to cancer patients. *Id.*

Herceptin cannot be administered to patients in its lyophilized form. Instead, the labeling instructs the purchaser (healthcare provider) to "[r]econstitute" the Herceptin drug product by injecting "20 mL of Bacteriostatic Water for Injection (BWFI)" into the Herceptin vial. AA839. This is supposed to "yield a multiple-dose solution containing 21 mg/mL trastuzumab" ("**Herceptin Solution**"). *Id.* The healthcare provider then administers the Herceptin Solution to the patient through an intravenous drip. AA836.

In September 1998, FDA approved Genentech's BLA for Herceptin. AA891. The BLA included a specification for drug product protein content. AA1507. Under that specification, a batch of Herceptin met the manufacturing acceptance criteria for "strength" or protein content if it contained 440 mg ± 35 mg of trastuzumab, *i.e.,* 405 to 475 mg. *Id.* From 1998 to 2017, Genentech sold the product in multi-dose Herceptin vials and packages that were labeled "440 mg." AA900. FDA approved the labels. AA891.

B. Starting in 2009, Genentech routinely put less than 440 mg trastuzumab in "440 mg" vials.

From 2000 through 2008, a majority of the Herceptin batches released in the United States contained at least 440 mg of trastuzumab per vial. AA1754, AA1762; District Court Opinion ("**Op**.") 7. In 2000, 2001, and 2006, over 82% of Herceptin

batches contained at least 440 mg of the drug in each vial. AA1762; Op. 7. In 1998 and 2005, ***all*** the measured batches met or exceeded the label claim. AA1762; Op. 7.

By 2009, the average protein content in Herceptin batches had dropped below 440 mg per vial and never again exceeded 440 mg. AA1732, AA1754; Op. 7. Over 80% of Herceptin batches tested after June 10, 2009 were underfilled. AA1737. In 2012 and 2014, ***none*** of the 89 Herceptin batches measured contained the labeled amount of trastuzumab. AA1762; Op. 7. For the three-year period of 2012-2014, only ***one*** of the 125 batches measured contained at least 440 mg trastuzumab per vial.[4] Op. 7. There is no evidence Genentech ever told FDA that it put less than the labeled amount of Herceptin in over 80% of its Herceptin packages from 2009 through 2017. AA1669, AA1670, AA1680.

C. FDA Guidances stated that lyophilized products like Herceptin should contain enough drug to allow healthcare providers to withdraw the labeled amount.

By early 2014, FDA was "concerned" that healthcare providers were using "unsafe handling and injection techniques" in administering injectable drugs, leading to "vial contamination and an increased risk of bloodborne illness transmission between patients." FDA Draft Guidance for Industry, *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*

[4] This decrease in the amount of trastuzumab in the Herceptin drug product correlates with a decrease in the concentration of the drug substance used to produce the drug product. AA1658, AA1750.

(March 2014) ("**Draft Guidance**"). AA1090. It identified "labeled vial fill sizes" as a factor that may have contributed to this problem. AA1089. So, in March 2014, FDA published the Draft Guidance, addressing "fill and packaging issues for injectable drug products," including products like Herceptin that "require reconstitution." *Id*. FDA stated that for such lyophilized products, each container should contain enough drug product to "permit withdrawal and administration of the labeled volumes." AA1090. The Final Guidance, issued in June 2015, incorporated this requirement. FDA Guidance for Industry, *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) ("**Final Guidance**") AA1110-17. It also added a statement reinforcing that for "drug products requiring reconstitution, the product should be designed to meet the label claim and acceptable overfill . . . ." AA1115.

D. Genentech developed a strategy to mislead healthcare providers who questioned the amount of trastuzumab in a Herceptin vial.

Genentech received [redacted] from healthcare providers regarding the amount of trastuzumab in Herceptin vials. AA2516. The inquiries focused on [redacted] AA2522. As early as 2002, Genentech [redacted] those making inquiries that [redacted] AA3176.

By 2014, these inquiries were so frequent that Genentech created a memo to help Genentech employees answer questions from healthcare providers regarding why they could not obtain the labeled amount from Herceptin 440 mg vials (the "**Q&A Memo**"). AA2527-31. According to the Q&A Memo, [redacted] AA2529-30 (emphasis added). In other words, the memo directed Genentech employees to inform those making an inquiry that [redacted].

A draft of the Q&A Memo also proposed the following question and answer:

[redacted]

AA2546.

[redacted]

Id. [redacted] AA2527-31.

E. FDA called the Herceptin label "misleading."

In September 2014, FDA requested a teleconference with Genentech to discuss complaints that healthcare providers could not recover 440 mg from Herceptin vials. FDA noted the original BLA submission for Herceptin stated that "the vial contains 440 mg of trastuzumab, but after reconstitution, the vial allows for recovery of '400 mg of HERCEPTIN drug product.'" AA1134, AA1530. FDA asked Genentech to "justif[y] [] the discrepancy between the label claim and the recoverable amount as initially provided in the BLA . . . ." AA1134, AA1530.

On October 30, 2014, FDA and Genentech held a teleconference on the issue. AA1132-36. FDA informed Genentech that it "did not agree [with Genentech] that the Herceptin label complies with 21 CFR 201.51(g)," *i.e.*, the misbranding regulation discussed above. AA1135; *see also* AA2661, AA2665. According to summaries of the teleconference prepared by Genentech, FDA told Genentech

"several times" that the Herceptin 440 mg label was "misleading." AA2675. FDA instructed Genentech that the Herceptin "label cannot claim more than can be extracted." AA1133; *see* AA1135 (noting that "vials should be labeled according to the actual amount of product that can be ***withdrawn*** from the vial" (emphasis added)).

In response, Genentech (falsely) told FDA the Herceptin label reflected "the amount contained within the vial." AA1135; *see also* AA1129-30, AA1133-34. Genentech characterized the end users' complaint as one relating to "extractab[ility]," *i.e.,* that end users could not extract 440 mg from a multi-dose Herceptin vial because various factors prevented them from withdrawing the full amount of drug in the vial. AA1124-35.

On December 5, 2014, Genentech provided its written response to FDA, proposing a label change that would "provide clarity" that a Herceptin vial might deliver less than 440 mg if used as a multi-dose vial. AA1130. There is no evidence that Genentech told FDA—either at the October meeting or in its written response—that healthcare providers could not recover 440 mg of trastuzumab because more than 80% of Herceptin vials contained less than that amount.

F. FDA rejected Genentech's proposed label change.

In February 2017, FDA rejected as "inadequate" the labeling change proposed by Genentech, noting that "the Herceptin vial does not contain sufficient content to

allow for recovery of 440 mg of a 21 mg/mL solution after reconstitution." AA1208. FDA recommended the "labeling for Herceptin be revised to 420 mg . . . ." *Id*. It did not propose any changes to the strength specification range, which remained 405 to 475 mg. *Id*.

FDA officials were [redacted] AA3095; *see also* AA3098, AA3103, AA3108. This position had been [redacted] AA3095. FDA took the position that it had [redacted] AA2114.

G. Genentech stopped making multi-dose Herceptin.

Genentech ceased production of Herceptin 440 mg vials in 2017. AA2124. It never produced any Herceptin vials labeled "420 mg." *Id*. Instead, Genentech switched to single-dose Herceptin vials labeled "150 mg." *Id.* Although FDA approved a protein content specification for the "150 mg" vial of [redacted] mg, AA3117-18, FDA requires Genentech to put no less than [redacted] mg of trastuzumab in the vials to ensure healthcare providers can withdraw the labeled amount. AA2047, AA2829-30.

IV. Procedural background

Because Herceptin 440 mg was a multi-dose vial, healthcare providers paid for at least 440 mg of the drug per vial but were unable to administer that amount to their patients. As a result, they could not obtain reimbursement for the full amount they paid for the drug, and Genentech reaped a windfall because it could sell more vials of Herceptin out of the same amount of drug product. To address this illegal scheme, Plaintiffs filed 14 separate cases throughout the country against Genentech based on the company's now-admitted practice of putting less than the labeled amount of Herceptin in multi-dose Herceptin vials. All Plaintiffs asserted claims for breach of warranty and unjust enrichment, and one Plaintiff also alleged additional state-law claims, including fraud. The Judicial Panel of Multidistrict Litigation consolidated the cases into this multidistrict litigation. Plaintiffs in two cases sought certification of a nationwide class.

Without holding a hearing on the motion, the district court granted summary judgment in favor of Genentech on March 20, 2019. It concluded federal law preempts Plaintiffs' state-law claims both on obstacle preemption and impossibility preemption grounds. The obstacle-preemption ruling rests on three bases: (1) the FDCA permits "reasonable variations" in drug contents; (2) the court found Herceptin to be a "solid" drug for purposes of 21 C.F.R. § 201.51(g), thus its label was required to state the "accurate net weight" of the drug within variations that

complied with the USP; and (3) in approving the BLA, FDA authorized Genentech to put as little as 405 mg of trastuzumab in Herceptin vials labeled "440 mg." Op. 14-19. Because Plaintiffs' claims would require the vials to contain at least 440 mg of trastuzumab, the district court concluded those claims would pose an obstacle to the objectives of this federal regulatory scheme. *Id.*

Relying on allegedly "undisputed" facts that had, in fact, been disputed in detail by Plaintiffs, the court determined that if Genentech were forced to meet its label claim, it would be required to change its manufacturing process in ways necessitating prior FDA approval. Op. 21-23 That led the court to conclude it would be impossible for Genentech to comply with the state-law duties alleged by Plaintiffs. *Id.* Plaintiffs filed this appeal.

STANDARD OF REVIEW

This Court reviews a summary judgment decision de novo, utilizing the same legal standards the district court should have applied. *See Dahl v. Charles F. Dahl, M.D., P.C. Defined Benefit Pension Tr.*, 744 F.3d 623, 628 (10th Cir. 2014). The Court must view the facts "in the light most favorable" to Plaintiffs and "draw all reasonable inferences" in their favor. *Smothers v. Solvay Chems., Inc.*, 740 F.3d 530, 538 (10th Cir. 2014) (internal quotation marks omitted).

SUMMARY OF THE ARGUMENTS

The district court concluded that federal law allowed Genentech to underfill over 80% of Herceptin 440 mg vials. On that basis alone, the court held that obstacle preemption barred Plaintiffs' state-law commercial claims. This ruling not only contradicts FDA's current construction of federal law, but it also improperly expands the scope and nature of federal preemption for state-law claims seeking to remedy drug-labeling misrepresentations. Under the district court's analysis, so long as a drug label complies with federal labeling laws, obstacle preemption will bar any state-law claim seeking to enforce commercial terms in the labeling. But the Supreme Court in *Wyeth* made clear that conduct is not insulated from liability under state law merely because it conforms to federal law. Regardless of whether Genentech was guilty of the federal crime of misbranding, it can still be held civilly liable under state law for misrepresenting the contents of Herceptin packages unless state law presents an obstacle to a federal purpose.

There is no federal purpose to which Plaintiffs' state-law claims present an obstacle. The federal misbranding statute and its legislative history do not reflect a congressional purpose adversely impacted by Plaintiffs' claims. The labeling regulation and alleged regulatory approvals relied upon by the district court lack the "clear and manifest" intent required to preempt the state-law commercial claims. And the ad-hoc agency actions cited by the court are not entitled to obstacle-

preemptive effect regardless. The district court's obstacle-preemption ruling cannot stand.

The district court's impossibility preemption analysis fares no better. The court reasoned that it was "impossible" for Genentech to comply with both federal and state law because, in its view, it was "undisputed" that Plaintiffs' state-law commercial claims required Genentech to make manufacturing changes that would have required prior FDA approval. This was doubly wrong: Genentech's claim that its only path to compliance would require FDA approval was both disputed and unsupported by the record. Genentech offered no evidence that Plaintiffs' claims mandated a specific change to the Herceptin manufacturing processes or specifications. In fact, Genentech made no effort to determine what changes, if any, would be necessary to meet its label claim.

Even Genentech's own internal data undermines its impossibility defense. It was certainly ***possible*** for Genentech to produce Herceptin vials containing between 440 and 475 mg trastuzumab, complying with both state law and the FDA-approved specification for Herceptin. How do we know? For some years early in its production of Herceptin, Genentech was able to comply with federal and state law in 100% of its tested lots. Genentech provided no evidence that either this compliance or the subsequent decline in trastuzumab vial content was the result of changes requiring prior FDA approval. Without proof that it could only comply with state law by

making changes requiring prior FDA approval, Genentech failed to establish impossibility preemption.

Finally, Plaintiffs also contend the Herceptin label misstates the concentration of the Herceptin Solution, requiring healthcare providers to use more of the drug than necessary to treat their patients. The district court applied obstacle preemption to this claim, too, without identifying any federal purpose to which the claim presented an obstacle. It also held the concentration claim to be barred by impossibility preemption, summarily stating that it was impossible for Genentech to change its label to state the accurate concentration without first obtaining FDA approval for the change. This analysis is not nearly enough to justify preempting state-law claims designed to hold drug companies accountable for misrepresentations on their labeling.

Congress left to the states the authority to enforce commercial promises made by drug companies. Because the district court's order disregards this congressional choice, the order should be reversed.

ARGUMENT

I. The presumption against preemption requires that Genentech prove Congress had a clear and manifest purpose to pre-empt state law.

The Supremacy Clause of the United States Constitution vests "Congress" with "the power to preempt state law." *Arizona v. United States,* 567 U.S. 387, 399

(2012). Thus, every preemption inquiry focuses on whether Congress intended to exercise this power. *See Wyeth*, 555 U.S. at 565 ("[T]he purpose of Congress is the ultimate touchtone in every pre-emption case." (internal quotation marks omitted)).

The Supreme Court has explained that "because the States are independent sovereigns in our federal system, we have long presumed that Congress does not cavalierly pre-empt state-law causes of action." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996); *see Ramsey Winch Inc. v. Henry*, 555 F.3d 1199, 1204 (10th Cir. 2009) ("Courts do not lightly attribute to Congress or to a federal agency the intent to preempt state or local laws." (internal quotation marks omitted)). This is particularly true where Congress has legislated in a field traditionally occupied by the States. In those cases, a court should "start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Lohr*, 518 U.S. at 485; *see Desiano v. Warner-Lambert & Co.,* 467 F.3d 85, 94-96, 98 (2d Cir. 2006) (declining to find "that Congress, without any explicit expression of intent . . . modified (and, in effect, gutted) traditional state law duties between pharmaceutical companies and their consumers"); *Ramsey Winch*, 555 F.3d at 1204 (noting the assumption that Congress did not intend to preempt state law "applies with greater force when the alleged conflict is in an area traditionally occupied by the States").

The consumer protection claims asserted by Plaintiffs fall within the state's historic power to protect its citizens. *See Castro v. Collecto, Inc.*, 634 F.3d 779, 784-85 (5th Cir. 2011) (recognizing "states have traditionally governed matters regarding contracts and consumer protections"); *Gen. Motors Corp. v. Abrams*, 897 F.2d 34, 41-42 (2d Cir. 1990) ("Because consumer protection law is a field traditionally regulated by the states, compelling evidence of an intention to preempt is required in this area."). As a result, Genentech bears the burden of establishing preemption and must overcome a "presumption against pre-emption." *Wyeth*, 555 U.S. at 565 & n.3; *see In re Methyl Tertiary Butyl Ether (MTBE) Prods. Liab. Litig.*, 725 F.3d 65, 96 (2d Cir. 2013). To do so, it must prove Congress had a "clear and manifest purpose" to pre-empt state law. *Wyeth*, 555 U.S. at 565 & n.3; *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) ("In areas of traditional state regulation, we assume that a federal statute has not supplanted state law unless Congress has made such an intention clear and manifest." (internal quotation marks omitted)). The district court failed to recognize—much less to apply—these guiding preemption principles.

II. The district court's conclusion that obstacle preemption barred Plaintiffs' state-law consumer-protection claims was wrong.

The district court held that obstacle preemption barred Plaintiffs' claims for damages for Genentech's failure to provide the amount of Herceptin promised on the Herceptin labeling. That was wrong. The court cited no statute or legislative

history demonstrating congressional intent to preempt state-law claims that seek to enforce commercial promises on prescription drug labels. That is because it is just the opposite. Congress intended to ***preserve*** state-law claims, like those at issue here, that protect consumers. The district court's contrary conclusion should be reversed.

A. The district court identified no federal purpose to which Plaintiffs' claims presented an obstacle.

The district court's belief that the claims in this case were impliedly preempted turned on its view that they "conflict with federal law" because federal law "permits reasonable variations for solid drugs sold in vials." Op. 16. But that is not enough to trigger preemption, for at least three reasons. *First*, the regulatory scheme that permits reasonable variations for the sale of solid drugs in vials establishes only a regulatory floor, not a ceiling, and so cannot preempt state laws that impose more stringent standards. *Second*, nothing in the at-issue regulation, statute, or legislative history establishes that Congress (or the FDA) intended to preempt state laws imposing higher (or different) standards on manufacturers selling solid drugs in vials. And *third*, the claims in this case do not eliminate or abridge any goal that the federal regulation seeks to promote. Because the claims in this case would not stand as an obstacle to any federal objective, the district court's pro-preemption conclusion should be reversed.

1. The commercial claims are not preempted merely because they may impose requirements more stringent than federal law.

It is well settled that obstacle preemption does not bar state-law claims merely because they impose standards more stringent than federal law. The Supreme Court's decision in *Wyeth* makes this clear. *See Wyeth,* 555 U.S. at 574-77. There, the plaintiffs alleged the manufacturer defendant (Wyeth) violated state law by failing to warn of certain risks in its drug labeling. Wyeth claimed FDA had deemed the warnings "sufficient" when it approved the labeling, thus providing Wyeth with "a complete defense" to the state-law tort claim. *Id.* at 558-59. It urged the Court to find that the "FDCA establishes both a floor and a ceiling for drug regulation" and that a state-law verdict cannot hold an FDA-approved label inadequate. *Id.* at 573-74.

The Supreme Court rejected this argument. Pointing to the legislative history of the FDCA (discussed above), the Court found that "all evidence of Congress' purposes is to the contrary." *Id.* at 574. As the Court explained, under the FDCA, Congress did not provide a federal remedy for consumers damaged by prescription drugs, but instead "determined that widely available state rights of action provided appropriate relief for injured consumers." *Id.* That was important: "If Congress thought state-law suits posed an obstacle to its objectives," the Court observed, "it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history." *Id*. But Congress's choice not to enact such a

provision, coupled with its "certain awareness of the prevalence of state tort litigation" provided "powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 575; *see also Merck Sharp*, 139 S. Ct. at 1677 (reiterating this view of the FDCA); *Hillsborough Cty. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 720-22 (1985) (finding no obstacle preemption where local ordinance imposed on plasma centers "requirements more stringent than those imposed by the federal regulations").

The same rationale applies here: Congress did not intend FDA—whose primary job is to ensure drug safety and effectiveness—to have sole authority to police drug companies' compliance with commercial terms and promises. *Wyeth*'s analysis applies with equal (or greater) force to claims challenging a drug manufacturer's commercial misconduct—even where the claims "touch[] upon an area dealt with by the FDA." *In re Epogen & Aranesp Off-Label Mktg. & Sales Practices Litig.*, 590 F. Supp. 2d 1282, 1290-92 (C.D. Cal. 2008) (declining to find commercial claims for false advertising impliedly preempted). The FDA's jurisdiction does not "extend . . . so far" as to "be responsible for resolving all questions of whether a statement made in connection with prescription drug advertising was false . . . ." *Id.* at 1292.

To conclude that state commercial claims are impliedly preempted therefore requires adopting "exactly the reasoning rejected in *Wyeth*." *In re Bayer Corp.*

Combination Aspirin Prods. Mktg. & Sales Practices Litig., 701 F. Supp. 2d 356, 375 (E.D.N.Y. 2010). That is because, even if "labeling meets the floor established by federal regulations, there is nothing to indicate that it could not still be misleading and therefore actionable under state consumer protection laws." *Id.* at 375-76. Thus, consumers may pursue claims for misrepresentations on drug labels under state consumer protection laws even if FDA "tacitly approved" those statements at some point in time. *Id.* at 375.

The district court failed to meaningfully consider these key preemption lessons. It attempted to distinguish *Wyeth* on the theory that the federal regulations in *Wyeth* "allowed the manufacturer of an anti-nausea medication to ***unilaterally*** strengthen warnings on the medication," while the regulation here permits a range of "reasonable variations."[5] Op. 17 (citing *Wyeth*, 555 U.S. at 568). This "distinction" is irrelevant when it comes to obstacle preemption. A drug manufacturer's ability to unilaterally change its label was crucial to the *Wyeth* court's decision regarding ***impossibility*** preemption. *See Wyeth*, 555 U.S. at 568. It played no role in the Supreme Court's obstacle-preemption analysis or its holding that state law may impose requirements on prescription drugs that are more onerous than federal law. The district court's effort to distinguish *Wyeth* fails. Genentech

[5] As shown below, Plaintiffs' claims would permit reasonable variations between 440 and 475 mg.

cannot escape state-law liability simply because Plaintiffs' claims involve warranties printed on an FDA-approved label and conduct that, according to the district court, did not violate federal law.

2. Plaintiffs' commercial claims do not pose an obstacle to any federal purpose.

Even putting aside the district court's mistaken understanding of *Wyeth*, its obstacle preemption analysis is flawed for another reason. The district court correctly recognized that obstacle preemption applies "if state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" Op. 11 (quoting *In re Universal Serv. Fund Tel. Billing Practices Litig.*, 619 F.3d 1188, 1196 (10th Cir. 2010)). But the court's application of this standard tripped at the threshold: it failed to identify any congressional purpose to which Plaintiffs' claims would pose an obstacle. That was error. The absence of any specifically identifiable congressional purpose means, *a fortiorari*, that the claims at issue here cannot pose any obstacle.

The key case relied on by the district court—*Jones v. Rath Packing Co.,* 430 U.S. 519 (1977)—demonstrates the court's error. There, three milling companies challenged a California statute requiring food packages to weigh at least the amount stated on the package at the time of sale. *Id*. at 522-23. In their view, the state law was preempted by the Fair Packaging and Labeling Act ("**FPLA**"), 15 U.S.C. § 1451, *et seq*. *Id.* at 541. The Supreme Court agreed, holding the state law was

impliedly preempted by the FPLA—not the FDCA—because specific evidence established that "a major purpose" of the FPLA was "to facilitate value comparisons among similar products." *Id*. at 541.

The Court's holding in *Jones* thus turned on the existence of a specifically identifiable congressional purpose of the FPLA to which enforcement of a state law would have posed an obstacle. The California law posed an obstacle to this statutory purpose, the Court explained, because it would require national manufacturers who sold in California to over-pack their flour packages to compensate for possible moisture (and weight) loss during distribution. *Id.* at 542-43. And doing that would mean that, if the law were enforceable, the contents of flour packages would differ depending on whether a brand of flour was sold in California, making it difficult for "consumers throughout the country . . . to compare the value of identically labeled packages of flour." *Id*. at 543 (concluding that California's law "would prevent 'the accomplishment and execution of the full purposes and objectives of Congress' in passing the FPLA").

This Court's obstacle-preemption case law reinforces the point. In *Chamber of Commerce of the United States v. Edmondson*, 594 F.3d 742 (10th Cir. 2010), for instance, the plaintiffs challenged parts of an Oklahoma act addressing illegal immigration. The Court held obstacle preemption barred a provision requiring contracting entities to "verify the work authorization status of independent

contractors." *Id.* at 769. Although noting that the federal Immigration Reform and Control Act ("**IRCA**") excluded independent contractors from verification obligations, the Court did not find obstacle preemption merely because state law imposed an obligation not found in the federal statute. Instead, the Court relied on the fact that Congress "intentionally excluded" the requirement from IRCA because it would "increase the burdens on business and could lead to increased employment discrimination." *Id.* at 767, 769 (noting that one of the purposes of the IRCA was to "limit employment discrimination"). The Court held that "[b]y requiring verification of independent contractors, Oklahoma risks exposing contracting entities to liability under federal [discrimination] law" and exposed them to an increased number of claims of unfair employment practices. *Id.* at 769. This was counter to the express purpose of Congress in the IRCA and thus barred by obstacle preemption.

These cases illustrate why there is no conflict here. For starters, although the district court relied heavily on *Jones*, Op. 15, it failed to recognize the key distinction between that case and this one. In *Jones*, it was the FPLA and its identifiable statutory goal of facilitating consumer value comparison—not the FDCA—that triggered obstacle preemption. The two statutes are not the same. They contain different provisions and were passed for different reasons. Because the FDCA lacks the type of relevant and identifiable congressional purpose that the Supreme Court

found in the FPLA, *Jones* undermines, rather than supports, the district court's conclusion.

Focusing on the actual statute at issue here—the federal misbranding statute, 21 U.S.C. § 352(b)—bears this out. Section 352(b) allows "reasonable variations" in the contents of some drug packages. But, at most, § 352(b) provides that a manufacturer does not commit a federal crime if the contents of its drug package reasonably vary around the labeled amount. There is no indication of congressional intent to similarly limit or prohibit state-law commercial claims relating to those package contents. There is certainly no evidence of a "clear and manifest purpose" to pre-empt state law, as required by *Wyeth*, 555 U.S. at 565 & n.3. Indeed, the history of the FDCA (discussed above) demonstrates a clear intent to leave state-law remedies available to plaintiffs who are harmed by a drug manufacturer's misconduct. Because there is no congressional purpose for the FDCA's allowance for reasonable variations with which Plaintiffs' claims allegedly interfere, the district court's preemption holding cannot stand.

The legislative history cited by the district court adds nothing to the case for preemption. The district court attempted to rely on legislative history for the 1913 amendments to the 1906 Act, suggesting Congress first permitted "reasonable variations" to excuse manufacturers from the requirement that packages contain "exactly" the amount stated on their labels. Op. 15. But that shows only that

Congress recognized the difficulty of manufacturing packaged products containing an ***exact*** amount of product. It does not suggest Congress intended to allow manufacturers to provide ***less than*** the labeled amount of a drug in a package.[6]

Plaintiffs do not allege Genentech must fill each vial with ***exactly*** 440 mg of trastuzumab—only that the vial must contain ***at least*** that amount. Under Herceptin's specification, a vial of Herceptin could contain up to 475 mg trastuzumab. Plaintiffs' claims would permit Herceptin vials to contain reasonable variations between 440 and 475 mg trastuzumab—which is entirely consistent with the congressional scheme set forth in the FDCA. As a result, the commercial claims in this case present no obstacle to the only even arguable federal purpose implicated by § 352(b), *i.e.,* avoiding the difficulty inherent in providing "exactly" the labeled amount.

The corresponding regulation, 21 C.F.R. § 201.51(g), which defines "reasonable variations" for purposes of the misbranding statute, exerts no preemptive effect on Plaintiffs' claims either. As the Supreme Court has explained, "because agencies normally address problems in a detailed manner and can speak through a variety of means, including regulations, preambles, interpretive statements, and responses to comments, we can expect that they will make their

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[6] FDA did not construe the statute to require reasonable variations below the labeled amount because its implementing regulation expressly requires that any variations in the package contents of liquid drugs must be sufficiently ***above*** the labeled amount to ensure withdrawal of the labeled amount. *See* 21 C.F.R. § 201.51(g).

intentions clear if they intend for their regulations to be exclusive." *Hillsborough Cty.*, 471 U.S. at 718; *see Utah Native Plant Soc'y v. United States Forest Serv.*, 923 F.3d 860, 868 (10th Cir. 2019) (applying assumption that "federal regulations do not preempt the States' exercise of [their] historic powers unless their intent to do so is 'clear and manifest'" and recognizing that "to say [a federal agency] may issue preemptive regulations is not to say it may do so subtly").

FDA expressed no such "clear and manifest" intent in promulgating § 201.51(g). The provision, included among the "Labeling Requirements for Prescription Drugs," just restates the FDCA's statutory requirement that drug packages contain an "accurate statement of the quantity of contents" and sets parameters for how the net contents of a drug package should be listed on a label to avoid federal criminal liability. *Id*. But nothing in this provision—or any other part of the regulatory scheme—expresses an intent to preempt state warranty or other consumer protection laws. And the district court did not cite any other evidence of FDA intent to displace state law through federal labeling requirements.

Instead, the district court relied on informal agency actions to support its conclusion. In the court's view, the FDA allegedly made a "determination" to approve the Herceptin BLA proposed by Genentech in 1998, which included a strength manufacturing range of 405-475 mg, and labeling promising "440 mg." Op. 6, 14, 17-18. The district court also cited anecdotal evidence that FDA approved

supplemental Herceptin applications in subsequent years that included data showing that some batches of 440 mg Herceptin contained less than the labeled amount. Op. 7. This reliance was improper.

First, ad hoc agency actions that are not subject to the notice-and-comment requirements for promulgating regulations have "insufficient procedural safeguards to elevate" those actions to "law that can have preemptive effect." *In re Santa Fe Nat. Tobacco Co. Mktg. & Sales Practices & Prods. Liab. Litig.*, 288 F. Supp. 3d 1087, 1219 (D.N.M. 2017) (holding consent order between FTC and cigarette manufacturer requiring manufacturer to include disclosure on cigarette label did not preempt state claims based on that label because a "voluntary agreement . . . between two parties, even when one is a federal agency, cannot 'blot out' a dual sovereign's law without procedural safeguards"); *see also Reid v. Johnson & Johnson*, 780 F.3d 952, 964 (9th Cir. 2015) (declining to give preemptive effect to a FDA letter that allegedly authorized the defendant manufacturer's label claims because, *inter alia*, the letter was not subject to notice and comment).

This Court reached the same conclusion in its recent decision in *Utah Native Plant Society*. There, environmental organizations challenged the United States Forest Service's denial of their request to remove mountain goats from part of the Manti-La-Sal National Forest. 923 F.3d at 863-65. The groups argued that federal law preempted a Utah state agency's decision to place mountain goats on state land

adjacent to the national forest. In support, they cited Forest Service documents, including the Manti-La-Sal National Forest Plan and the applicable Research Natural Area establishment record. This Court gave those documents no preemptive effect, holding that they "d[id] not carry the force of law." *Id.* at 868 n.5 (citing *Christensen v. Harris Cty.*, 529 U.S. 576, 587 (2000) as "distinguishing agency adjudications and notice-and-comment rulemaking, both of which have the force of law, from opinion letters, policy statements, agency manuals, enforcement guidelines, and the like, all of which lack the force of law").

Here, FDA approved the BLA and Herceptin labeling without any of the procedural safeguards required for promulgating regulations. The public received no notice of the BLA or the proposed labeling and had no opportunity to comment on their contents. Nor was there any opportunity for the public to challenge those approvals through either administrative or judicial review. These ad hoc approvals—known only to Genentech and FDA for decades—do not have the force of law and cannot preempt state law.

Second, there is no evidence FDA expressly considered in 1998 whether Genentech could sell vials of Herceptin containing less than 440 mg of trastuzumab in packages labeled "440 mg."[7] The "determination" relied upon by the district court

[7] FDA examined the issue in 2014 and determined Genentech must include at least enough Herceptin per vial to allow healthcare providers to ***withdraw*** 440 mg. This requires the vial ***contain*** at least that amount.

is implicit at best. These are separate regulatory actions—*i.e.*, approval of a specification range of 405 to 475 and approval of labeling promising "440 mg"—knitted together by the district court to find preemption. These ad hoc approvals do not support the district court's conclusion. *See, e.g., Gustavsen v. Alcon Labs., Inc.*, 903 F.3d 1, 14 (1st Cir. 2018) (declining to give deference to prior ad hoc decisions "made by mid-level FDA scientists, or even a single 'reviewer'" and evidence of "FDA inaction," which could mean that "FDA used its discretion not to enforce a rule, or that a company otherwise slipped through the cracks") (cited in Op. 12, 21).

Even taken together, these independent actions could not compel preemption. That is because, even if it could be said that FDA intended to permit Herceptin vials to contain as little as 405 mg despite the label claim ***and*** even if such actions could validly be considered evidence for preemptive effect, the district court cited ***no intent*** by FDA to preempt state-law consumer-protection claims based on that underfill. The district court thus erred in basing its obstacle-preemption holding on this regulatory history.

B. **The federal regulatory scheme is consistent with Plaintiffs' claims.**

The district court's error is compounded by the fact that its basic premise was wrong: federal law ***does not*** permit the underfill challenged by Plaintiffs. The regulation and Herceptin's regulatory history undermine, rather than support, the case for preemption.

1. FDA's current position regarding Genentech's obligation to provide the labeled amount of Herceptin comports with the claims in this case.

The FDA's current position is what matters for preemption purposes. *See Abbot by Abbot v. Am. Cyanamid Co.,* 844 F.2d 1108, 1114 (4th Cir. 1988) ("The point of time that is relevant in deciding whether a federal policy requires preemption . . . is the time of the suit."). And here, beginning in 2014, FDA has made clear its position that Genentech must provide ***more than*** 440 mg of trastuzumab in Herceptin vials labeled "440 mg"—a position that is fully consistent with the claims in this case.

In 2014, FDA issued the Draft Guidance, stating that lyophilized products like Herceptin should be labeled to reflect the minimum quantity of drug product that can be withdrawn from the vial. AA1086-1092. FDA finalized the Guidance and this instruction in 2015. AA1110-17. Also in 2014, FDA told Genentech its Herceptin label was "misleading" and ultimately required it to change the label to "420 mg" on the premise that all vials would deliver a minimum of 420 mg.[8] What that means for preemption purposes is clear: Plaintiffs' claims demand no more of Genentech than FDA does.

[8] Although Genentech claims FDA knowingly permitted Genentech to put as little as 405 mg in a vial, there is no evidence it ever told FDA that over 80% of Herceptin multidose vials did not contain 440 mg and some did not even contain 420 mg.

The district court lost sight of this. It found Plaintiffs' claims presented an obstacle based on a federal purpose that the agency charged with enforcing federal labeling laws ***does not have***. The court made this determination based on its conclusion that FDA changed its position on this issue in 2014. But that conclusion is contradicted by FDA itself, which took the position that it had [redacted] AA2114. Even if it were true that the agency changed its position, that would not matter because a court is bound to undertake its preemption analysis based on the prevailing federal purposes at the time the preemption issue is decided. So, in other words, obstacle preemption applies only if the pursuit of Plaintiffs' claims ***in this lawsuit*** would pose an obstacle to a current federal purpose. Because the FDA's current position is consistent with the claims here, there can be no obstacle preemption.

2. Plaintiffs' claims allege conduct that violates the regulation.

Even on its own terms, the district court wrongly concluded that the claims at issue in this case are inconsistent with, and so preempted by, FDA's controlling regulation. The regulation permits "[r]easonable variations caused by . . . unavoidable deviations in good manufacturing practice." 21 C.F.R. § 201.51(g). These variations must comply with the limitations of the U.S. Pharmacopeia, a compendium of drug information. Because Genentech did not establish that the

regulation permits its practice of underfilling over 80% of Herceptin vials, Plaintiffs' claims do not conflict with § 201.51(g).

First, Genentech did not prove it used good manufacturing practice. Federal regulations specify current Good Manufacturing Practices, which require drug manufacturers to formulate batches of drug product with the "intent to provide not less than 100 percent of the labeled or established amount of active ingredient." 21 C.F.R. § 211.101(a). The regulations required Genentech to adjust its manufacturing processes if it could not consistently provide at least 100% of the trastuzumab promised on the label. AA1861.

Although more than 80% of Herceptin 440 mg lots fell below the label claim from June 2009 to 2017, Genentech did not take adequate steps in its manufacturing processes to remedy this shortage. AA1652-55, AA1732-54, AA1861, AA2120-23. To the contrary, Genentech was content with low drug product strength and cared only that the vials fell within the specification range. AA1654-55, AA2118-27. This consistent failure to formulate batches of Herceptin to provide at least 440 mg trastuzumab—and Genentech's claimed indifference to it—undermines Genentech's assertion that it complied with the misbranding regulation. As a result, the district court erred in holding that Plaintiffs' state-law claims sought to impose liability on Genentech for conduct § 201.51(g) permitted. Instead, there is a genuine issue of material fact as to whether Genentech used good manufacturing practice and

whether its practice of underfilling the vast majority of Herceptin 440 mg vials violated the applicable federal regulations, as well as state law.

Second, Genentech did not prove the Herceptin underfill resulted from "***unavoidable*** deviations in good manufacturing practice." 21 C.F.R. § 201.51(g) (emphasis added). Genentech only offered evidence that it was not [redacted]. AA1507 (emphasis added). It did not challenge the feasibility of providing ***at least*** 440 mg of trastuzumab per vial, which is what Plaintiffs seek. AA1654-55, AA2123. In fact, Genentech affirmatively argued it [redacted][9] AA1507. Because the variations in protein content below 440 mg were not the result of "unavoidable deviations in good manufacturing practice," the regulation did not permit the contested underfill. At the very least, there are issues of disputed fact on this issue. If Genentech's conduct constituted misbranding under federal law, then imposing state-law liability for the same conduct could not be preempted.

Finally, the regulation requires the package label for solid drugs to state the "accurate net weight" of the drug. 21 C.F.R. § 201.51(g). Any variations in that weight must comply with the USP. *Id*. The district court held the USP "provides for

[9] This was the basis for Genentech's argument on impossibility preemption, which also fails for the reasons shown in Part III below.

an allowable variation of 15 percent from the stated weight." Op. 5 (citing USP General Chapter <905>, *Uniformity of Dosage Units*). However, the cited section of the USP applies to "solids . . . that are packaged in single-unit containers," AA1497, not multi-dose presentations like 440 mg Herceptin. So, even if the district court correctly held that Herceptin should be treated as a solid drug (despite FDA's decision that the standard for liquid drugs applies to Herceptin), Genentech violated the federal regulation by failing to state the accurate net weight on the Herceptin label. The same conduct subjects Genentech to liability under ***both*** federal and state law, and preemption cannot apply.

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For each of the above reasons, the district court erred in holding that Plaintiffs' claims present an obstacle to a federal purpose.

III. The district court erred in holding impossibility preemption bars Plaintiffs' state-law claims.

The district court made another fundamental error: it held that Plaintiffs' claims were barred under impossibility preemption. This holding is based on an incorrect premise—that it was "undisputed" Genentech could not have made the changes to its "manufacturing and specifications" that were necessary "to ensure that all Herceptin vials contained at least 440 mg" without first obtaining approval from FDA. Op. 21. The record does not support this assertion. Genentech did not prove, as a matter of law, that it could only meet the Herceptin label claim by taking actions

requiring prior FDA approval. Under the "demanding" standard that impossibility preemption will only bar those state-law claims that would impose a duty on a defendant "to take some action that is prohibited under federal law," the district court's conclusion should be reversed. *Schrock v. Wyeth, Inc.*, 727 F.3d 1273, 1286 (10th Cir. 2013); *see Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963) (holding that to establish impossibility preemption, a defendant must prove that "compliance with both federal and state [law] is a physical impossibility").

A. Genentech did not prove "major" changes were required to satisfy the label claim.

The district court held that impossibility preemption applied because it believed it was "undisputed" that Genentech would have been required to "make changes to manufacturing and specifications—both necessitating prior FDA approval—to ensure that all Herceptin vials contain at least 440 mg." Op. 21. That conclusion was neither undisputed nor accurate. Genentech failed to prove that changes requiring prior FDA approval were necessary to comply with state law.

1. Impossibility preemption applies only if state law would require "major changes" to manufacturing.

Federal regulations require drug manufacturers to inform the FDA if they make certain types of changes in their manufacturing process after a drug application is approved. *See* 21 C.F.R. § 601.12. The type of communication required depends

on the likelihood the proposed change will have an "adverse effect" on the "identity, strength, quality, purity, or potency of the product" as it relates to the safety or effectiveness of the product. *Id.* § 601.12(a)(2).

- "Major" manufacturing changes present a "substantial potential" to have an "adverse effect." *Id*. § 601.12(b). They require the manufacturer to submit a prior approval supplement ("**PAS**") to FDA and obtain FDA's approval for the change. *Id.*
- Changes with a "moderate" potential for an "adverse effect" may be made by giving FDA notice of the changes through a "Changes Being Effected in 30 Days" notice ("**CBE**"). *Id.* § 601.12(c)(1).
- "Minor" changes with a "minimal potential to have an "adverse effect" may be made immediately and described in the manufacturer's annual report. *Id*. § 601.12(d).

State law is preempted only if it would require "major changes" to the defendant's manufacturing process and would require submission of a PAS. *Compare Wyeth*, 555 U.S. at 573 (holding impossibility preemption did not apply because manufacturer could have used a CBE to make label changes sought by the plaintiffs) *with Gustavsen*, 903 F.3d at 10, 14 (applying impossibility preemption to bar state-law claims that sought change to a drug product container system, which was defined as a major change under the regulation).

2. Genentech did not prove that a "major" manufacturing change was the only way to satisfy Plaintiffs' demands.

Deciding whether a "major change" is necessary cannot occur in a vacuum. Courts must consider ***the specific change*** the plaintiffs' claims would require. Here,

the district court's ruling appears to be based on its belief or assumption that Genentech could not have changed the target fill weight for Herceptin without prior FDA approval. Op. 21. Even if this were correct (and, as explained at Part III.A.3, it is not), Genentech offered ***no proof*** that the ***only way*** to ensure compliance with state law was to make this alleged "major" change.

In support of its holding that state law would require a major change, the district court relied only on the declaration of Genentech employee Dana Swisher. Op. 9-10 (citing AA1507-08). Mr. Swisher claimed [redacted] AA1507. But Mr. Swisher acknowledged he made ***no attempt*** to determine ***why*** the vast majority of Herceptin batches measured after 2009 contained less than the labeled amount of trastuzumab. AA1654-55, AA2120-21. He also failed to conduct any experiments to determine whether Genentech could modify its manufacturing process within the FDA-approved requirements to make Herceptin vials that more consistently contained at least 440 mg trastuzumab. AA1654-55, AA2123. These admissions are fatal to Genentech's argument and require reversal of the district court's holding, which is based solely on Mr. Swisher's declaration. There is no basis for concluding that Plaintiffs' claims would require "major" manufacturing changes when the person who provided the only evidence to that effect—by his own admission—did not know

what caused the underfill or whether there were ways in which Genentech could remedy it without "major changes" to its manufacturing process.

By contrast, the plaintiffs in *Gustavsen* specifically complained that manufacturers of prescription eye drops "deliberately designed their [eye drop] dispensers to emit unnecessarily large drops." 903 F.3d at 5. The court in that case expressly recognized that state law would "mandate" that the eye drop dispensers be changed "to reduce the size of the eye drops." *Id.* at 6. The court then examined whether the defendants could modify the design of the dispenser to comply with state law without prior FDA approval. *Id.* at 10-14. It concluded that changing the dispenser to reduce the size of the eye drops would constitute a "'[c]hange[] in a drug product container closure system that controls the drug product delivered to a patient,'" which FDA regulations identify as a "major" change requiring FDA prior approval. *Id.* at 11 (quoting 21 C.F.R. § 314.70(b)(2)(vi)).

Plaintiffs have not sought a specific manufacturing change, and Genentech did not prove that it could comply with state law only by making a specific change. The district court erred in holding, as a matter of law, that Plaintiffs' claims demanded a "major" manufacturing change and that Genentech had satisfied the "demanding" standard for impossibility preemption.

3. The district court erred in holding Genentech could not change the target fill weight without prior FDA approval.

Even if Genentech could only meet the label claim for 440 mg Herceptin by changing the target fill weight, this change would not require prior FDA approval.[10] Although the Herceptin specification permits Genentech to include as much as 475 mg trastuzumab per vial, the court held Genentech could not target any fill weight above [redacted] mg because fill weight is an "in-process specification identified in the BLA" and changing it "requires prior FDA approval." Op. 21. The district court made no finding that targeting a fill weight above [redacted] met the criteria for a "major" change under the regulations, *i.e.,* that the change had a "substantial potential" to have an ***adverse effect*** on the "identity, strength, quality, purity, or potency of the product" as it relates to the safety or effectiveness of the product. It could not have such potential because ***FDA already approved distribution of vials containing up to 475 mg*** of trastuzumab. Merely targeting a weight higher in the FDA-approved range presents ***no*** risk to the safety or effectiveness of Herceptin, and the district court cited no evidence to the contrary.

[10] The district court appeared to reference the target fill of [redacted] mg of ***drug product*** per vial, which differs from the target fill weight for the ***drug substance*** that is put into each vial prior to lyophilization. The opinion mirrors arguments in Genentech's summary judgment reply, which specifically discusses a "target fill weight" of [redacted] mg of drug product. *Compare* Op. 21 *with* AA3250.

Instead, the district court based its decision on the irrelevant declaration of Genentech's expert witness and inapposite authorities. None support the court's conclusion. *First*, the district court cited testimony of Genentech's expert that does not support this proposition. Op. 21 (citing AA3128). Further, whether a change requires prior FDA approval is an issue of law, on which expert testimony is not permissible. *See United States v. Vreeken*, 803 F.2d 1085, 1091 (10th Cir. 1986) ("[Q]uestions of law are . . . not the subject of expert testimony.").

Second, the district court cited two regulations. Op. 21. Neither supports the court's conclusion. The first only states the general rule that changes to specifications typically require prior FDA approval. 21 C.F.R. § 601.12(b)(2)(i). It is the second regulation that purportedly characterizes certain requirements regarding drug product "'weight variation'" as "'in-process specifications.'" Op. 21 (quoting 21 C.F.R. § 211.110(b)). But the "weight variation" referenced in the regulation is expressly limited to "tablet or capsule weight variation." 21 C.F.R. § 211.110(a)(1). Herceptin is not sold in either tablet or capsule form, so this regulation does not apply.

Third, the district court relied on *Thompson v. Allergan USA, Inc.*, 993 F. Supp. 2d 1007 (E.D. Mo. 2014). Op. 21. There, the plaintiff sought a decrease in the fill volume for vials of eye drops. 993 F. Supp. 2d at 1009-10. Citing an FDA

Guidance,[11] that court determined the plaintiff's claims would require a change to the specifications, thus requiring prior FDA approval. *Id*. at 1014. There is no indication the plaintiffs sought a change in the fill volume that was ***within*** the specification range FDA already had approved. By contrast, Plaintiffs' claims would have required Genentech to limit its Herceptin sales in the United States to vials that met the target of the FDA-approved manufacturing range (440 mg) or fell within the upper half of that range (440 to 475 mg). The range itself could have remained unchanged.

Finally, the district court cites *Gustavsen* for the proposition that prior FDA approval was required where the plaintiffs "assert[ed] that eye drop manufacturer's practice of using eye drop dispensers that emit unnecessarily large drops was unfair." Op. 21. As discussed above, the *Gustavsen* plaintiffs alleged the hole that dispensed the eye drops in the FDA-approved ***container*** was too large. 903 F.3d at 4-5. The requested alteration constituted a change to a "drug product container closure system that controls the drug product delivered to a patient," which is expressly deemed a

[11] The district court separately cited the same 2001 FDA Guidance. Op. 21. The guidance does not discuss adjustments of the target fill within an approved range. AA3429. Moreover, FDA issued a new draft guidance in December 2017 which states that "[c]hange in the fill volume" for a drug product can be accomplished through a CBE. FDA Draft Guidance for Industry, *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* at 29 (Dec. 2017). AA3213.

"major" change. *Id.* at 11-12 (quoting 21 C.F.R. § 314.70(b)(2)(vi)). Plaintiffs do not request any change to the Herceptin container, so *Gustavsen* does not apply.

Bottom line: The district court's conclusion that prior FDA approval would be required to adjust the target fill within the approved specification range is erroneous and should be reversed.

B. **Genentech's data showed it could meet—and actually had met—the Herceptin label claim without making major manufacturing changes.**

The district court also identified an alternative reason to support its impossibility-preemption conclusion: that Plaintiffs' state-law claims would essentially force Genentech to stop selling some of its Herceptin vials. Op. 22 (concluding that the claims, if successful, would permit Genentech to sell "only those vials that contain at least 440 mg of trastuzumab."). It held that "Genentech cannot be forced to stop selling vials that comply with FDA requirements in order to avoid liability under state law." Op. 23. However, preventing Genentech from selling Herceptin vials that do not comply with state law would not require Genentech to "to take some action that is prohibited under federal law." *Schrock*, 727 F.3d at 1286. Impossibility preemption therefore does not apply.

The evidence shows that Genentech was selling some batches of Herceptin vials that complied with both state and federal law. State law requires at least 440 mg of trastuzumab per vial, while the FDA-approved specifications for Herceptin

set an outer strength limit of 475 mg. In 1998 and 2005, ***all*** tested batches of Herceptin fell within this range. Genentech offered ***no evidence*** of any FDA-approved manufacturing changes that enabled it to meet the label claim in all of the tested lots in those years, but not in others. Even after the Herceptin protein content levels fell in 2009, Genentech was still able to include between 440 and 475 mg trastuzumab in almost 20% of the Herceptin 440 mg batches. AA1652, AA1732. It was indisputably ***possible*** for Genentech to ***produce*** Herceptin vials containing between 440 and 475 mg of trastuzumab without changing anything about its manufacturing process. By selling only those vials, Genentech could have complied with both state law and federal law, which ***did not*** require Genentech to ***sell*** Herceptin vials in the United States containing less than 440 mg trastuzumab.

Mutual Pharmaceutical Co. v. Bartlett, 570 U.S. 472 (2013) does not change this conclusion. In that case, the Supreme Court reversed the First Circuit's decision that a generic drug manufacturer could comply with both its federal and state-law duties by ceasing to sell a drug that was defectively designed. The Court held its preemption cases "presume that an actor seeking to satisfy both his federal- and state-law obligations is ***not required to cease acting altogether*** in order to avoid liability." *Id.* at 488 (emphasis added).

But here, unlike the claims in *Bartlett*, Plaintiffs' claims do not assert a design defect that necessarily occurs throughout all production lots. Because some lots of

Herceptin met or exceeded the 440 mg label claim, Plaintiffs' claims would not have required Genentech to "cease acting altogether," *i.e.,* to stop producing Herceptin 440 mg. They merely would have mandated that Genentech limit its domestic sales to those lots of "440 mg" Herceptin containing at least 440 mg of the drug. Manufacturers routinely are forced to discard or re-purpose batches of prescription drugs that fail to comply with the specifications for the drug or are otherwise ineligible for distribution. The district court's holding that state-law claims cannot prevent a manufacturer from selling even ***a single lot*** of product that conforms to FDA's requirements impermissibly extends *Bartlett* beyond its limits. Under the court's holding, no state law could ever force defendants to conform their conduct to more stringent standards than what federal law requires. Such a rule squarely conflicts with *Wyeth*. *See* Part II.A.1 above.

The district court misunderstood the question at the heart of impossibility preemption. The relevant question is ***not*** whether it was ***desirable***—as a matter of public policy—to prevent Genentech from selling batches of Herceptin that federal law allowed it to sell. The question is whether it was ***physically impossible*** for Genentech to manufacture vials of Herceptin that met its label claim and to limit its domestic sales to those vials. The evidence shows it was not. The district court erred in holding that Genentech met the demanding standard for impossibility preemption.

C. It was possible for Genentech to increase the protein content of Herceptin vials without prior FDA approval.

Despite the district court's failure to recognize it, it is ***Genentech's*** burden to prove it was impossible to provide at least 440 mg of trastuzumab in Herceptin 440 mg vials without making changes requiring prior FDA approval. *See, e.g.*, *Merck Sharp*, 139 S. Ct. at 1678 (explaining that "impossibility pre-emption is a demanding defense" and requires that a manufacturer provide "clear evidence" that federal law actually prohibited the manufacturer from changing its label). As shown above, Genentech failed to meet that burden for numerous, independent reasons, and summary judgment should have been denied on those bases.

Plaintiffs were ***not*** required to prove it was possible for Genentech to comply with both state and federal law. Nonetheless, they introduced substantial evidence showing Genentech could increase the protein content of 440 mg Herceptin through adjustments to (1) drug substance concentration, and/or (2) the target fill weight for the drug substance. AA1655-60, AA1711-13, AA1732-33, AA1746, AA1750-57, AA1763, AA2366, AA2402-05, AA2407-09, AA1462, AA1662, AA2430-43, AA2445-55, AA2458-69, AA2471-72. ***Genentech did not argue these adjustments would have required prior FDA approval***. AA3252-53. Instead, it claimed Plaintiffs had not shown the changes would ensure 440 mg in ***every*** vial. AA3253. As shown above, this is not the standard for impossibility preemption, nor is it Plaintiffs' burden to prove. The district court failed even to mention these possible adjustments

in its Opinion. It certainly offered no reason why the largely unrefuted evidence, showing the feasibility of the proposed adjustments, did not create an issue of fact precluding summary judgment. This failure, too, requires reversal.

IV. Preemption does not bar Plaintiffs' claims for misrepresentations regarding the concentration of Herceptin Solution.

In addition to their claim for Genentech's failure to provide the promised 440 mg of trastuzumab, Plaintiffs seek damages for Genentech's misrepresentations regarding the concentration of the reconstituted Herceptin Solution. This misrepresentation caused Plaintiffs to purchase more Herceptin to treat their patients. The district court erred in holding the concentration claim was preempted by both obstacle and impossibility preemption.

A. Obstacle preemption does not bar the concentration claim.

Genentech's obstacle-preemption argument is based on federal labeling requirements for indicating the "net quantity of contents." *See* 21 U.S.C. § 352(b); 21 C.F.R. § 201.51(g). It cited no federal statute or regulation governing labeling requirements for statements of drug concentration, nor did FDA approve a specific concentration level for reconstituted Herceptin in the BLA. AA1650, AA2134. Genentech cited no congressional purpose relating to statements of concentration. Yet, the district court applied obstacle preemption, repeating its reasoning for holding ***the underfill claim*** to be preempted. Op. 20. This holding—which offers no basis for preempting ***the concentration claim***—should be reversed.

B. Impossibility preemption does not apply because it was possible for Genentech to change its label to state the accurate concentration.

The district court also applied impossibility preemption to the concentration claim, summarily holding that "changing the concentration stated on the label . . . would require FDA approval." Op. 22 (citing 21 C.F.R. § 601.12(f)(1)). However, impossibility preemption does not bar claims seeking changes to drug labels where, as here, the manufacturer can make the necessary changes through a CBE. *Wyeth*, 555 U.S. at 571.

A CBE can be used to "add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product." 21 C.F.R. § 601.12(f)(2)(i)(C). FDA has instructed manufacturers to utilize this provision to "[c]larif[y] the administration statement to ensure proper administration of the product." AA3174. Plaintiffs sought a change to the "Dosage and Administration" section of the USPI, specifically the provision titled "Preparation for Administration." AA836, AA839, AA1029, AA1032, AA1650. Genentech could have changed its label to "ensure proper administration" of Herceptin without prior FDA approval.

This change was "intended to increase the safety of the use of the product." 21 C.F.R. § 601.12(f)(2)(i)(C). Some healthcare providers used the overfill in the diluent vial to compensate for the lack of Herceptin Solution, and FDA cautioned this practice could [redacted] AA1669, AA2661, AA2784.

Taking measures to improve the accuracy of the dosing administered to patients would have increased the drug's safety.

The labeling change sought by Plaintiffs also reflected "newly acquired information," as required for a CBE. 21 C.F.R. § 601.12(f)(2)(i). As early as 2002, Genentech had learned the label misstated the concentration of Herceptin Solution. AA2238. Genentech continued to receive complaints from healthcare providers that they could not recover the warranted amount of Herceptin Solution, AA1664, AA2516, AA2522, AA3176, AA3179, and continued to recognize the inaccuracy of the concentration statement on the label, AA1650-51, AA2225, AA2239, AA2268, AA2341. This information was sufficient to permit and require Genentech to correct the Herceptin vial label without prior FDA approval.

Because Genentech could have changed the concentration statement with a CBE, Genentech cannot prevail on its impossibility preemption defense without clear evidence FDA would not have approved that change. *See Wyeth*, 555 U.S. at 571. Genentech offered ***no*** evidence FDA would have prevented the change. The district court's ruling that it was impossible for Genentech to correct the concentration misrepresentation on the Herceptin label should be reversed.

CONCLUSION

Plaintiffs' efforts to hold Genentech to the commercial promises made in its labeling do not present an obstacle to any federal purpose. Nor was it "impossible" for Genentech to provide the warranted 440 mg of medication in Herceptin vials sold in the United States. Genentech merely chose not to do so. The court should reverse the summary judgment and remand the case for trial on the issue of whether Genentech violated state law by failing to provide the promised amount of trastuzumab in the vast majority of Herceptin vials sold during the relevant time period.

Dated: July 31, 2019

Respectfully submitted,

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REASONS WHY ORAL ARGUMENT IS NECESSARY

Oral argument is necessary because this case presents important and complex issues of law and fact. Plaintiffs seek damages of hundreds of millions of dollars in this multi-district litigation involving 17 oncology practices throughout the country and a putative nationwide class. The district court entered summary judgment in Genentech's favor based on two theories of implied federal preemption. Oral argument will benefit this panel and is important to Plaintiffs as they seek their day in court to be heard on the merits of their substantial claims.

Dated: July 31, 2019

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CERTIFICATE OF COMPLIANCE

I certify, pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C), that the attached Appellants' Opening Brief:

(1) complies with Federal Rules of Appellate Procedure 28(a) and 32(a)(7)(B), because it contains 12,917 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii); and

(2) complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5), and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2016, in 14-point Times New Roman font.

Dated: July 31, 2019

/s/ David L. Bryant
David L. Bryant, OBA No. 1262

ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OKLAHOMA

IN RE: GENENTECH, INC.,	)	
HERCEPTIN (TRASTUZUMAB)	)	MDL DOCKET NO. 16-MD-2700
MARKETING AND SALES	)	
PRACTICES LITIGATION	)	

OPINION AND ORDER

Before the Court is the Amended Motion for Summary Judgment Based on Federal Preemption (Doc. 201) filed by defendant Genentech, Inc. ("Genentech"). Plaintiffs oppose the motion.

I. Introduction

Genentech manufactures, markets and distributes Herceptin® (hereafter, "Herceptin"), a biologic drug used to treat breast cancer. Plaintiffs are cancer treatment providers who have purchased Herceptin for treatment of their patients. Plaintiffs do not challenge the efficacy or safety of the drug, but contend that Herceptin's labeling is misleading because, although the Herceptin label states that each vial contains 440 mg of Herceptin at a concentration of 21 mg/mL, not every vial contains that amount or more. They assert California state law claims for breach of express and implied warranties and unjust enrichment, and they seek actual damages, costs and attorneys' fees. Doc. 45 at 13-20. Genentech, in its Motion for Summary Judgment, contends that Plaintiffs' claims are preempted by federal law.

II. Background

Federal law gives the Food and Drug Administration ("FDA") the authority and responsibility to regulate prescription drugs. *See* 21 U.S.C. § 301 *et seq*. The FDA regulates virtually every aspect of the manufacturing, distribution, evaluation and labeling of drugs marketed and sold in the United States. *See Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 237 (2011) (noting pervasive regulation of vaccine licensing). The FDA drug approval process is "onerous and lengthy." *Mutual Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 476 (2013).

Biologics[1] such as Herceptin are similarly regulated. *See* 21 U.S. § 321(g)(1). Before a biologic product can be distributed, the FDA must approve the sponsor's biologic license application ("BLA"). 21 U.S.C. § 355(b), 42 U.S.C. §262(a). The BLA contains "specifications" for the product, which establish criteria for determining whether each lot of the biologic satisfactorily conforms to the drug product, as approved by the FDA. 21 C.F.R. § 211.165(a). It also includes data from studies showing that the product meets prescribed requirements for safety, purity and potency; a full description of manufacturing methods; data establishing product stability; samples of the product, labeling, and containers; and summaries of product test results. *Id.*, §§ 601.2(a), 600.3(kk). Manufacturers of biologic products are required to test each lot of the product for, *inter alia*, potency, safety, purity and sterility. *Id.*, §§ 610.10, 610.12-14. If a lot does not meet the specifications, it cannot be distributed to the public and must be rejected. *Id*., § 211.165(f).

The FDA will approve a BLA only if it determines that the manufacturer's biological product and facilities comply with federal regulations. *Id.*, § 601.4. Essentially, a biologics license

[1] Biologics are drugs made from complex molecules manufactured using living microorganisms, plants or animal cells.

reflects the FDA's determination that the product is safe, pure and effective, and that the manufacturer's facilities and processes are adequate to meet these high standards. *Id.*, § 601.2(d).

The biologic product's accompanying labeling must also conform to federal law. 21 U.S.C. §§ 331(a), 352; 21 C.F.R. § 601.2(a). The FDA will approve a BLA only if it finds that the drug is "safe for use" under the conditions "prescribed, recommended, or suggested in the proposed labeling," and it will approve the labeling only if it is not "false or misleading in any particular." 21 U.S.C. § 355(d)(1) & (7).

Additionally, applicants must notify the FDA about "each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s)." 21 C.F.R. § 601.12(a). Prior FDA approval is usually required for labeling changes, particularly if the proposed change would affect the information that must appear in the Highlights of Prescribing Information section of the physician package insert. *Id.*, § 601.12(f)(1) (citing § 201.57(a)).

III. Statement of Undisputed Material Facts

Twenty to thirty percent of breast cancers are known to have amplification of a growth factor receptor gene known as HER2, and women whose breast cancers have a high level of expression of this gene have a shortened survival rate. Doc. 201-2, Def. Ex. 2 at 7. Herceptin—known generically as trastuzumab—is a prescription drug that helps stop the cancer's growth by targeting HER2 protein. Doc. 201-1, Def. Ex. 1 at 2. Trastuzumad's effect in fighting this aggressive form of cancer has been described as "dramatic," and trials have shown that addition of the drug to chemotherapy "resulted in a remarkable 50% reduction in disease recurrence compared with patients receiving chemotherapy alone." Doc. 201-3, Def. Ex. 3 at 3, Korkaya, H.,

et al., *HER2 and Breast Cancer Stem Cells: More than Meets the Eye*, 73 *Cancer Research* 3489-93 (June 15, 2013)).

Herceptin is a biologic product produced from living organisms—namely, Chinese hamster ovary cells that have been genetically modified to produce trastuzumab, the active ingredient. Doc. 201-5, Def. Ex. 5, Dec. of Dr. David T. Lin, ¶30; Doc. 201-6, Def. Ex. 6, Dec. of Dana L. Swisher, ¶¶ 5-7. Its production begins in large bioreactor tanks with modified cells replicating in a culture medium and producing trastuzumab. *Id.*, Swisher Dec., ¶ 7. Eventually, the protein trastuzumab is harvested from the cells, a process involving several purification steps to remove cell debris and other unwanted elements. *Id.* The resulting protein solution is referred to as the "drug substance." *Id.* The drug substance is tested to ensure the protein concentration is within the FDA-approved range of 25 milligrams per milliliter (mg/mL), plus or minus 1 mg/mL. *Id.*, ¶ 8. If the drug substance concentration is outside the approved range, the batch is rejected. *Id.* If it is within the approved range, it is frozen for storage and shipping. *Id.*

Tanks of frozen Herceptin drug substance are shipped to manufacturing facilities, where they are thawed and tested again to ensure the concentration is still within the FDA-approved range of 25 mg/mL ± 1mg/mL. *Id.*, ¶9. From there, one or more tanks of Herceptin substance may be pooled. *Id*. Generally, the next step prior to filling is sterile filtration. *Id.*, ¶10. During this step, the drug substance passes through a sterilization-grade filter and on to the fill line. *Id.* The drug substance is then filtered, sterilized and dispensed into glass vials by filling machines. *Id.*, ¶ 11. The target fill weight for each vial is 17.92 grams, but the FDA-approved acceptable outer range is 17.56 to 18.28 grams, *i.e.* 17.92 g ± 2%. *Id*. A range around the target fill weight of 17.92 grams is necessary because the filling equipment is incapable of filling every vial with precisely 17.92 grams. *Id*.

The vials of drug substance are lyophilized or freeze-dried, removing most of the water and leaving what is known as the Herceptin "cake," comprised of the dry solid protein and some inactive ingredients. *Id.*, ¶12. The FDA-approved specification for protein content of the drug product is 440 mg± 35mg/mL per vial. *Id.*, ¶12. After the vials are filled and sealed, sample vials are submitted to Quality Control, where they undergo final testing prior to release for distribution. *Id.*, ¶13. The sample vials are identified in the Certificate of Analysis ("COA"). *Id.* The protein content of the vials is tested in accordance with protocol Q12398. *Id.* ¶¶13, 16.

Because the precise concentration of the drug substance and the precise fill weight varies from batch to batch, the weight of the Herceptin cake in each vial will also vary in a range around 440 mg. *Id.*, ¶ 14. When shipped, each vial of Herceptin is accompanied by a vial of sterile water that providers use to dissolve the powder cake—a process known as reconstitution. *Id.*, Doc. 201-1, Ex. 1, Highlights of Prescribing Information.

The FDA approved the BLA for Herceptin on September 25, 1998. Doc. 201-4, Def. Ex. 4. The BLA provides for Herceptin drug substance concentrations within a range of 25 mg/mL ± 1mg/mL and drug product levels within a range of 440 mg ± 35 mg. *Id.* The FDA also approved Herceptin labeling that claimed 440 mg per vial, recognizing in subsequent correspondence with Genentech that the "expected recovery from each vial is approximately 19 mL or 400 mg." Doc. 377-1, Def. Ex. 13. Additionally, in 1999, the FDA drafted a letter to providers explicitly referring to the fact that the vials were designed to deliver 400 mg. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶¶47-49 (citing Def. Ex. 13, *supra*). US Pharmacopeia ("USP") General Chapter <905>, *Uniformity of Dosage Units,* provides for an allowable variation of 15 percent from the stated weight. *Id.*, Lin Dec., ¶ 29 and Ex. D thereto, p. 494, Table 2.

Plaintiffs' own data show that:

- Herceptin drug substance concentrations have always complied with the FDA-approved range of 25 mg/mL ± 1 mg/mL, and
- Herceptin drug product levels always complied with the FDA-approved range of 440 mg± 35 mg.

Doc. 368, Pls.' SOF 5, 10, 26.

The term "nominal" in prescription drug labeling refers to a "theoretical" amount, signaling that the actual amount in each vial will vary. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶ 36; Doc 377-2, Def. Ex. 14 at 145:20-146:8.

The Prescribing Information[2] states that Herceptin is shipped in multi-dose vials "nominally containing 440 mg Herceptin as a lyophilized, sterile powder." Doc. 201-1, Def. Ex. 1, Highlights of Prescribing Information at 1. Similarly, the carton for each vial states that "the nominal content of each HERCEPTIN vial is 440 mg Trastuzumab." *Id.*, Doc. 201-7, Def. Ex. 7. This description in labeling is consistent with the FDA-approved specification of 440 mg ± 35 mg and the variability permitted under FDA regulations. *Id.*

The Herceptin carton and vial labels state that reconstitution will "yield a multiple-dose solution containing approximately 21 mg/mL Trastuzumab." 201-7, Def. Ex. 7; Doc. 201-8, Def. Ex. 8. The concentration is "approximately" 21 mg/ml because the actual concentration depends on the amount of Herceptin in each vial, which varies, and the amount of sterile water a provider injects during reconstitution, which also varies. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶¶ 38-40, 43. Additionally, each vial of Herceptin contains a residual and variable amount of moisture—up to three percent—that may be lost over time due to absorption by the stopper on the vial. *Id.*, ¶ 33.

[2] Prescribing Information is a detailed description of a drug's uses, dosage range, side effects, drug-drug interactions and contraindications that is available to clinicians and included in pharmaceutical packaging instructions.

For each year from 2000 through 2008, a majority of the Herceptin batches released in the United States contained at least 440 mg of trastuzumab. Doc. 368 at 16, Pls. SOF 10. In 2000, 2001, and 2006, more than 82 percent of Herceptin batches contained at least 440 mg of trastuzumab, and in 1998 and 2005, 100 percent of batches met or exceeded the label claim. *Id.* Pls.' SOF 11. However, the proportion of batches containing at least 440 mg of trastuzumab dropped below 50 percent by 2009 and has not exceeded 50 percent since then. *Id.*, Pls. SOF 10. Only one of the 125 batches tested in the three-year period of 2012-2014 contained at least 440 mg of trastuzumab per vial, and in 2012 and 2014, none of the 89 Herceptin batches tested contained 440 mg or more. *Id.*, Pls. SOF 10-11, 14. Nevertheless, at no time from 1998 to 2017 did *any* batch contain less than the lower limit of 405 mg of trastuzumab approved by the FDA. Doc. 201-6, Def. Ex. 6, Swisher Dec., ¶14.

Between the FDA's initial approval of Herceptin on September 25, 1998, and February 3, 2017, the FDA approved more than 10 supplemental applications from Genentech proposing revisions to the Herceptin Prescribing Information without ever directing Genentech to change the description of net weight or concentration. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶ 50. For example, on October 12, 2012, Genentech submitted a prior approval supplement to the FDA requesting approval for the Hillsboro Technical Operations manufacturing facility to manufacture 440 mg vials. Doc. 377-13, Def. Ex. 25. The supplement included data on three qualification batches of Herceptin drug product, and the protein content for all three batches was below 440 mg. Doc. 377-14, Def. Ex. 26. The FDA approved the supplement on February 14, 2013. Doc. 377-15, Def. Ex. 27. On June 6, 2014, the FDA approved a supplement for a manufacturing facility, that also included data on three qualification batches for which the protein content was below 440 mg. Doc. 377-16, Def. Ex. 28.

In March 2014, the FDA published a Draft Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products. Doc. 370-31, Pls. Ex. 31. The Draft Guidance stated that "with respect to allowable excess volume, the sponsor/applicant of drugs in ampules or vials, intended for injection must follow the requirements in 21 CFR 201.51(g)."[3] The Draft Guidance was finalized in June 2015. Doc. 370-34, Pls. Ex. 34.

On October 30, 2014, after the FDA received complaints from an unidentified oncology pharmacy specialist and other oncology institutions about the inability of end users to withdraw a full 21 mL volume from a vial of Herceptin, FDA and Genentech representatives conducted a teleconference. Doc. 201-9, Def. Ex. 9 at 2. During the teleconference, the FDA asked Genentech to provide a formal written response addressing the FDA's concerns regarding labeling of the Herceptin 440 mg multi-dose vial. *Id*. at 4.[4] The FDA also proposed that in order to provide further clarity, the Herceptin 440 mg label should be revised to reflect the maximum amount that can be withdrawn from the vial, in accordance with the agency's interpretation of 21 C.F.R. § 201.51(g), as reflected in the 2014 Draft Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, March 2014. Doc. 201-9, Def. Ex. 9, Resp. to FDA's Comments Regarding Herceptin 440 mg Multi-Dose Vial Fill at October 3, 2014 Teleconference, at pp. 3-4.

[3] 21 C.F.R. 51(g) states, in pertinent part, "In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the *minimum quantity*. . . (emphasis added).

[4] Plaintiffs contend in their Statement of Facts that the FDA "told Genentech 'several times' that the Herceptin 440 mg labeling was 'misleading." Doc. 368 at 33. To clarify, however, the Court notes that the FDA made all such statements during the October 30, 2014, teleconference between FDA representatives and Genentech personnel, and it appears that this was the first time FDA ever raised such concerns. Doc. 370-54, Pls.' Ex. 54 at 3.

Approximately a month later, in its December 5, 2014, response, Genentech proposed the addition of language stating that recovery of Herceptin may be lower when the 440 mg vial is used as a multi-use vial. *Id.* at 4-5. The FDA did not reply to Genentech's response until February 3, 2017—more than two years after Genentech submitted proposed labeling changes. Doc. 201-10, Def. Ex. 10. During that time, in April 2015 and March 2016, it approved two unrelated labeling supplements that did not change the way net contents were described. Doc. 201-5, Def. Ex. 5, Lin Decl., ¶¶ 58, 71 n. 68.

In its February 3, 2017, Advice Letter, the FDA disagreed with Genentech's proposed labeling changes and directed the company to submit a plan to address revision of the labeling from 440 mg per vial to 420 mg per vial on all labeling and to prepare a communication plan to educate healthcare practitioners on the labeling change. Doc. 201-10, Def. Ex. 10.

Genentech submitted a response to the letter on February 10, 2017. *Id.*, Doc. 201-11, Def. Ex. 11. In its response, Genentech agreed to "update the Herceptin USPI of the previously referred to as the '440 mg' strength to the 420 mg strength that reflects the minimally recoverable volume for the Herceptin vial presentation;" to "commit to providing updated carton/container labeling as a Post-Marketing Commitment," and to "provide an updated communication plan at the time the revised carton/container are submitted." *Id.* The FDA approved the supplemental BLA the same day. *Id.*, Doc. 201-12, Def. Ex. 12.

If Genentech were required to ensure that every vial contained exactly (or at least) 440 mg of Herceptin, it would have to either change its manufacturing processes—including filling and lyophilization, and possibly the amount of diluent for reconstitution—and seek FDA approval for a protein content specification that deviates from the currently approved range of 440 mg ± 35

mg., or—as Plaintiffs suggest—stop selling vials that fail to meet the approved range. Doc. 201, Def. Ex. 6, Swisher Dec., ¶ 15; Doc 368 at 68-69.

The manufacture of Herceptin is an aseptic (sterile) processing operation, and substituting steps in an aseptic processing operation is a "major change" requiring FDA approval. Doc. 377, Ex. 17, U.S. BLA Herceptin, GENE-FL0000000527-529, 55521; C.F.R.§ 601.12(b)(2)(vi). Moreover, changing the target fill rate, which is an in-process specification identified in the BLA, also requires prior FDA approval. Doc. 377, Def. Ex. 14, Lin Dep. at 151:1-25; 21 C.F.R. § 601.12(b)(2)(i) (referencing changes in qualitative or quantitative formulation or in the specifications provided in the approved application). *See also* 21 C.F.R. §211.110(a)(), (b) (referencing "in-process specifications" applicable to drug product "weight variation"); Ex. 22, FDA Guidance for Industry, *Changes to an Approved NDA or ANDA, Questions and Answers*, at 9 (Jan. 2001) ("A change in the fill volume of a drug product involves a change to the specification and must be submitted in a prior approval supplement.").

IV. Standard for Summary Judgment

Summary judgment is proper only if "there is no genuine issue as to any material fact, and the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). The moving party bears the burden of showing that no genuine issue of material fact exists. *See Zamora v. Elite Logistics, Inc.*, 449 F.3d 1106, 1112 (10th Cir. 2006). The Court resolves all factual disputes and draws all reasonable inferences in favor of the non-moving party. *Id.* However, the party seeking to overcome a motion for summary judgment may not "rest on mere allegations" in its complaint but must "set forth specific facts showing that there is a genuine issue for trial." Fed. R. Civ. P. 56(e). The party seeking to overcome a motion for summary judgment must also make

a showing sufficient to establish the existence of those elements essential to that party's case. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 323-33 (1986).

V. Preemption Law

Preemption analysis requires the court to compare federal and state law. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 611 (2011). If a private party cannot comply with state law without first obtaining the approval of a federal regulatory agency, the application of the state law to that private party is preempted. *Id.* at 620 (stating that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."). The Court's "inquiry into the scope of a [federal] statute's pre-emptive effect is guided by the rule that the purpose of Congress is the ultimate touchstone in every pre-emption case." *Hughes v. Talen Energy Mktg., LLC*, 136 S. Ct. 1288, 1297 (2016) (citing U.S. Const., Art. VI, cl. 2 and *Altria Group, Inc. v. Good*, 555 U.S. 70, 76 (2008)).

Preemption may be express or implied. Implied preemption may take the form of either obstacle preemption—which is applicable if state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress"—or impossibility preemption—which is applicable if it would be "impossible for a private party to comply with both state and federal requirements." *In re Universal Service Fund Telephone Billing Practice Litig.*, 619 F.3d 1188, 1196 (10th Cir. 2010). The federal requirements may be imposed by federal statutes or regulations. *See Fid. Fed. Sav. & Loan Ass'n. v. de la Cuesta*, 458 U.S. 141, 153 (1982). The state law subject to preemption may be state statutes, regulations, or duties imposed by tort claims or other court actions. *See Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324-25 (2008); *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861, 881 (2000).

Impossibility preemption is applicable when a private party cannot "*independently* do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing,* 564 U.S. 604, 620 (2011)

(citing *Wyeth v. Levine*, 555 U.S. 555, 573 (2009) (emphasis added)). In other words, "[i]f a private party . . . cannot comply with state law without first obtaining the approval of a federal regulatory agency, then the application of that law to that private party is preempted." *Gustavsen v. Alcon Laboratories*, 903 F.3d 1, 9-10 (lst Cir. 2018).

VI. Analysis

Plaintiffs' Third Amended Complaint alleges Genentech has breached warranties and violated California consumer protection statutes by falsely claiming that (1) each Herceptin vial contains 440 mg of trastuzumab; (2) if a vial of Herceptin is reconstituted according to defendant's instructions, it will yield a solution with a concentration of 21 mg/mL of trastuzumab (the "Solution"); and (3) each vial of reconstituted Herceptin contains 20.952 mL of solution. Plaintiffs challenge the accuracy of Herceptin's labeling concerning the amount of trastuzumab in the vials, whether measured as weight, volume or weight per milliliter.[5]

Genentech contends that Plaintiffs' claims are impliedly preempted because they seek to impose (1) a state-law requirement that would stand as an obstacle to the federal regulatory scheme, which recognizes reasonable variation in manufacturing and labeling must be allowed (*i.e.*, "obstacle preemption") and (2) a state-law duty on Genentech to change either its manufacturing processes or its Herceptin labeling, neither of which it can do under federal law without prior FDA approval ("impossibility preemption").

Specifically, Genentech argues Plaintiffs' state-law claims present an obstacle to the federal regulatory scheme for branding of prescription drugs—*i.e.*, 21 U.S.C. § 352(b) and 21

[5] Milligrams (mg) measure weight, and one mg is 1/1000 of a gram; milliliters (ml) measure volume of liquid, and one ml is 1/1000 of a liter; and mg/mL measures milligrams per milliliter.

C.F.R. § 201.51(g).[6] It asserts that (1) Herceptin complies with federal labeling laws, which allow for reasonable variations in manufacture and labeling; and (2) Plaintiffs may not use state law claims to impose a more stringent standard than federal law allows. Additionally, Genentech contends that Plaintiffs' claims are barred by impossibility preemption because, in order to meet Plaintiffs' demands, it would have to change either the product labeling or the reconstituted solution volume—both of which would require FDA approval.

Plaintiffs, however, argue that neither obstacle preemption nor impossibility preemption bar their claims because the FDA has incorrectly regulated Herceptin as a "solid drug" rather than a "liquid drug;" the FDA's 2014 Draft Guidance stating that the labeling of all injectable drugs, including those reconstituted from a solid, should be applied retroactively; and Herceptin did not

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[6] 21 U.S.C. § 352(b) states that a drug shall be deemed misbranded--:

> If in package form unless it bears a label containing . . . (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count: *Provided*, That under clause (2) of this paragraph **reasonable variations shall be permitted**, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary. (emphasis added).

21 C.F.R. § 201.51(g) states:

> The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large. In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. **In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.** (emphasis added).

meet § 201.51(g)'s allowance for "[r]easonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing."

A. Obstacle Preemption

Genentech argues all of Plaintiffs' claims are barred because they impose an obstacle to the FDA's "reasonable variations" determination and are inconsistent with federal law. Plaintiffs assert obstacle preemption is inapplicable because (1) their claims do not conflict with federal law; (2) Genentech is violating federal law; and (3) even if the Court grants summary judgment on their net weight claims, their concentration and solution volume claims should survive, because neither obstacle preemption nor impossibility preemption apply to the remaining two claims.

1. Plaintiffs' Claims Impose an Obstacle to the FDA's "Reasonable Variations" Determination

Federal law prohibits the manufacture, introduction or delivery of any drug that is adulterated or "*misbranded.*" 21 U.S.C. § 331(a), (g) (emphasis added).

Although package labels must contain "an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count," the applicable statute permits "reasonable variations" pursuant to regulations prescribed by the FDA. 21 U.S.C. § 352(b)(2). FDA regulations, in turn:

- permit "reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice;"
- provide that, "in the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight;" and
- state that "[v]ariations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary."

21 C.F.R. § 201.51(g). *Id.*

With respect to packaged food and drugs, the Supreme Court has recognized there is no way to completely eliminate variations in weight, and that to require strict precision would make it impossible to sell packaged products. In *Jones v. Rath Packing Co.*, it stated:

> It being apparent to everyone that it is impossible to make packages of exactly the same size or to pack them with exactly the same quantity of contents, and it being also apparent that the exact weight and measure of the contents of a package may undergo slight changes from natural causes, it is also apparent that legislation requiring similar packages to contain the same exact quantity in term of weight or measure, without allowing for any variation, would be destructive and prevent the putting of foods in packages.

430 U.S. 519, 5367, n.28 (1977) (quoting H.R. Rep. No. 850, 62d Cong., 2d Sess., at 2; S. Rep. No. 1216, 62d Cong., 3d Sess., at 2-3). In *Jones*, a meat processor and flour millers argued a California statute and regulation pertaining to the labeling by weight of packaged foods were preempted by federal laws regulating net weight labeling. The Court interpreted those regulations to mean that "[u]nder the FDCA, *reasonable variations from the stated net weight do not subject [the defendant] to prosecution, whether civil or criminal*, if the variations arise from the permitted causes." *Id.* at 536 (emphasis added). The Court stated:

> Since 1914, regulations under the food and drug laws have permitted reasonable variations from stated net weight resulting from packing deviations or gain or loss of moisture occurring despite good commercial practice. If Congress had intended to overrule this longstanding administrative practice, founded on a legislative statement of necessity, we would expect it to have done so clearly. Instead, it explicitly preserved existing law, with "no changes."

Id. at 537. Accordingly, the Court held that enforcement of more stringent state law was preempted because it would "prevent the accomplishment and execution of the full purposes and objectives of Congress . . ." *Id.* at 543.

FDA regulations provide that the labeling for a prescription drug must include a statement of the net quantity of contents. 21 C.F.R. § 201.51(a). The declaration of net quantity allows for reasonable variations because of loss or gain of moisture during the course of good distribution

practice and unavoidable deviations in good manufacturing practice. *Id.*, §210.51(g). The variations must comply with the limitations of the USP or the *National Formulary. Id.*

The description of the net quantity of contents required by FDA regulations depends on how the drug is supplied. Injectable drug products may be liquids in the form of solutions, emulsions or suspensions, or dry solids that are to be combined with an appropriate liquid to yield a solution or suspension.[7] FDA net quantity labeling regulations distinguish between liquid and solid drugs:

> The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. *Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized.* Variations from stated quantity of contents shall not be unreasonably large. *In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight.* Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.

21 C.F.R. § 201.51(g) (emphasis added). Thus, while the label for liquid drugs must express the *minimum* quantity, the label for Herceptin—a solid drug—is considered to express the "accurate net weight" of the drug.

Here, as in *Jones*, Plaintiffs' labeling claims conflict with federal law, which permits reasonable variations for solid drugs sold in vials. Nor is the Court swayed by Plaintiffs' assertion that *Wyeth v. Levine*, 555 U.S. 555 (2009) compels a different conclusion. In *Wyeth*, the Supreme

[7] Doc. 201-5, Ex. 5, Lin Dec., ¶26 (citing FDA Guidance for Industry (Draft), Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, p. 11, April 2013; FDA-CDER-SBIA Regulatory Education for Industry, Prescription Drug Labeling – Challenges and Issues: Common Deficiencies in Container Labels and Carton Labeling for Biological Products, November 2015.

Court held that a plaintiff's failure-to-warn claims were not preempted because federal regulations allowed the manufacturer of an anti-nausea medication to *unilaterally* strengthen warnings on the medication. *Id.* at 568. Here, in contrast, the regulatory scheme expressly allows a range of "reasonable variations" for solid drugs sold in vials, and Plaintiffs' state-law claims conflict with these regulations.

2. Plaintiffs' Claims are Inconsistent with Federal Law

a. Herceptin is a Solid Drug

Plaintiffs argue that Herceptin should be considered a "liquid drug" subject to the requirement that the label "express the minimum quantity" as a measure of volume, rather than as a "solid drug." However, regulatory history establishes that the FDA has always considered Herceptin to be a "solid drug." The FDA approved the BLA with a label that referenced a net weight of 440 mg and a fill weight specification allowing deviations both above and below 440 mg. (Doc. 377-14, Def. Ex. 14, Dep. of David T. Lin, at 139:2-12 ("When [Herceptin] was approved in 1998, FDA treated it as a solid drug."). Moreover, the FDA has repeatedly approved this labeling for nearly two decades, and when it approved the updated labeling in 2017, it inserted the phrase "for injection" next to the product name "HERCEPTIN® (trastuzumad),"[8] thereby reaffirming that it considers Herceptin to be a solid drug. Doc. 377-15, Def. Ex. 15.[9]

[8] The U.S. Pharmacopeia National Formulary distinguishes between drugs that are designated "injection" and those designated "for injection." "Injection drugs" are "[l]iquid preparations that are drug substances or solutions thereof," while "for injection drugs" are sold as "[d]ry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections. Doc. 372-10, Pls. Ex. 80 at 3.

[9] Plaintiffs also argue that even if Herceptin is a "solid drug" for purposes of § 201.51(g), Genentech has not proven it exercised "good manufacturing practice" with respect to the drug product strength, the variations in Herceptin strength were reasonable, or variations below 440 mg of trastuzumab were caused by "unavoidable deviations in good manufacturing," and therefore

b. The FDA's 2014 Draft Guidance is not Retroactive

Plaintiffs also contend that the Court should give deference to the FDA's conclusion in 2014 that Herceptin labeling did not comply with the 2014 Draft Guidance, in which it stated that the labeling of all injectable products, including those reconstituted from a solid, must reflect the minimum quantity of drug product that can be withdrawn from the vial. However, this argument is based on Plaintiffs' faulty premise that the Draft Guidance merely restated standards in place since the FDA originally approved Herceptin's BLA in 1998. As the regulatory history of Herceptin establishes, this is not true.

Moreover, from a legal stand point, Guidances are prospective in nature absent a contrary instruction from the FDA. Doc. 201-5, Ex. 5, Lin Dec., ¶¶62-71.[10] The Draft Guidance itself states that its recommendations "apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), as well as new packaging supplement to these existing applications submitted to CDER and CBER." Doc. 368-31, Pls. Ex. 31, FDA Draft Guidance for Industry, *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biologic Products*, at 1 (March 2014). Here, there is no dispute that the BLA for Herceptin was approved more than 15 years before the 2014 Draft Guidance was issued.

Finally, Plaintiffs' argument ignores Herceptin's approval history. The uncontroverted facts establish the FDA-approved BLA disclosed that although the protein content label claim was 440 mg, the vials were intended to deliver only 400 mg, and that in 1999, the FDA drafted a letter

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Genentech's Motion for Summary Judgment must be denied. Doc. 368 at 50. However, these arguments clearly go to the merits of Plaintiffs' claims rather than the issue of preemption.

[10] The Draft Guidance states that "[t]his draft guidance, when finalized, will represent the [FDA's] current thinking on this topic. It does not create or confer any right for or on any person and does not operate to bind FDA or the public." Doc. 368-31, Pls. Ex. 31, p. 1.

to providers explicitly referring to the fact that the vial was designed to deliver 400 mg. It was not until 2014 that the FDA raised concerns about the labeling of Herceptin, and although Genentech promptly submitted proposed revisions, the FDA waited until 2017 to respond to Genentech's proposal.[11]

Accordingly, the Court declines to apply the FDA's Draft Guidance retroactively.

c. Herceptin's Protein Content Variations Satisfied FDA Regulatory Requirements

Net quantity labeling for solid drugs is governed by 21 C.F.R. § 201.51(g), which states:

> The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. *Reasonable variations caused by loss or gain of moisture during the course of good distribution practice by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large.* In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation of above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. *In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.*

(emphasis added). The regulatory history of Herceptin clearly establishes that the FDA considers it to be a solid drug. It is undisputed that the protein content of the Herceptin 440 mg vials has always been within the total protein specification of 440 mg ± 35 mg (405 mg to 475 mg) approved by the FDA. Thus, at all relevant times, Genentech complied with the unambiguous terms of Section 201.51(g).

[11] Arguably, retroactive application of the 2015 Final Guidance to impose tort liability would violate due process. *See United States v. AMC Entm't*, 549 F.3d 760, 768-70 (9th Cir. 2008) (rejecting retroactive application of government's interpretation of ADA regulations to movie theaters).

d. Herceptin Was Not "Adulterated"

Plaintiffs argue that Herceptin is adulterated under 21 U.S.C. § 341 because "its strength differs from . . . that which it purports or is represented to possess." Doc. 368 at pp. 45-46 (quoting Ex. 81, FDC Compliance Policy Guide ("CPG") § 420.100). However, CPG § 420.100 provides: "[t]he applicable quality standards for a drug not recognized in an official compendium can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications." *Id.*

In this case, the FDA-approved Prescribing Information does not state that Herceptin vials contain exactly 440 mg, but instead that they "*nominally* contain[] 44 mg Herceptin." Doc. 201-1, Ex. 1 at 1 (emphasis added). Likewise, since at least April 2000, the carton label has stated that "[t]he *nominal* content of each HERCEPTIN vial is 440 mg Trastuzumab." Doc. 201-7, Ex. 7 (emphasis added).

3. Plaintiffs' "Concentration" and "Solution Volume" Claims Do Not Survive

The Court rejects Plaintiffs' arguments that Herceptin is a "liquid drug" rather than a "solid drug," and that it should be subjected to the "liquid drug" requirement that the labeling "express the 'minimum quantity' as a measure of volume" instead of the "solid drug" requirement that the labeling "express accurate net weight" with USP-compliant variations. The undisputed facts establish that the FDA has always treated Herceptin as a solid drug, and has allowed reasonable variations as provided in the USP. Additionally, USP General Chapter <905>, *Uniformity of Dosage Units*, provides for an allowable variation of 15% around the label claim. 21 C.F.R. § 201.51(g). Def. Ex. 5, Lin Dec. ¶29, Ex. D to Lin Dec. at 491. Therefore, like their "net weight" claim, Plaintiffs' "concentration" and "solution volume" claims also fail.

Accordingly, Plaintiffs' claims are barred by obstacle preemption.

B. Impossibility Preemption

Plaintiffs contend Genentech could comply with its state law-based demands by changing either the manufacturing process or the labeling of Herceptin.

Genentech, however, argues that Plaintiffs' claims fail as a matter of law under the doctrine of impossibility preemption, because ensuring that each vial contains exactly (or at least) 440 mg, as Plaintiffs demand, would have required Genentech to change its manufacturing process, its protein content specification and its labeling, all of which would require prior FDA approval.

It is undisputed that Genentech would be required to make changes to manufacturing and specifications—both necessitating prior FDA approval—to ensure that all Herceptin vials contained at least 440 mg. Changing the target fill weight, which is an in-process specification identified in the BLA, requires prior FDA approval. Doc. 377, Ex. 14, Lin Dep. at 141:1-25; 21 C.F.R. § 601.12(b)(2)(i); 21 C.F.R. § 211.110(a)(1)(b) (referencing "in-process specifications" applicable to drug product "weight variation"); Doc. 377, Ex. 22, FDA Guidance for Industry, *Changes to an Approved NDA or ANDA, Questions and Answers*, at 9 (Jan. 2001) ("A change in the fill volume of a drug product involves a change to the specification and must be submitted in a prior approval supplement. . . ."). *See also Gustavsen*, *supra* (affirming district court's dismissal of case asserting that eye drop manufacturer's practice of using eye drop dispensers that emit unnecessarily large drops was unfair and resulted in unjust enrichment because the manufacturing changes plaintiffs sought would require prior FDA approval); *Thompson v. Allergan U.S.A., Inc.*, 933 F. Supp. 2d 1007, 1013-14 (E.D. Mo. 2014) (granting motion to dismiss based on federal preemption because changing the fill volume in each vial of eye drops would require prior FDA approval).

Plaintiffs also suggest that Genentech could have changed from the originally approved static filling process to a variable filling method to ensure 440 mg per vial. Doc. 368 at 79 (citing Ex. 2, Ramirez Dec., ¶¶ 32-33). However, this would still require prior FDA approval because the manufacture of Herceptin is an aseptic (sterile) processing operation. Doc. 377, Ex. 17, GENE-FL0000000527-529, 555. Substituting steps in an aseptic processing operation is a "Major change" requiring prior FDA approval. 21 U.S.C. § 601.12(b)(2)(vi). Additionally, Defendant would be required to change the Herceptin labeling to reflect the change in diluent volume. *See* 21 C.F.R. § 601.12(f)(1); Doc. 201, Ex. 5, Lin Dec., ¶¶ 75-76.

Finally, Plaintiffs contend that Genentech could have changed its label to state the accurate concentration for reconstituted Herceptin solution. Changing the concentration stated on the label, however, would require FDA approval. 21 C.F.R. § 601.12(f)(1). Similarly, changing the concentration of the reconstituted drug product would also require FDA approval because it would have "a substantial potential to have an adverse effect on the . . . strength [and] potency" of Herceptin and affect the "safety or effectiveness of the product." 21 C.F.R. § 601.12(b)(1) and (2)(i).

C. Stop Selling

Finally, Plaintiffs argue that Genentech could comply with state law by keeping its manufacturing process the same, but selling only those vials that contain at least 440 mg of trastuzumab. Doc. 368 at 68-69. This "stop-selling" argument, however, was squarely rejected in *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013). There, the Supreme Court stated:

> Our pre-emption cases presume that an actor seeking to satisfy both his federal-and state-law obligations is not required to cease acting altogether in order to avoid liability. Indeed, if the option of ceasing to act defeated a claim of impossibility, impossibility pre-emption would be "all but meaningless."

> The incoherence of the stop-selling theory becomes plain when viewed through the lens of our previous cases. In every instance in which the Court has found impossibility pre-emption, the "direct conflict" between federal- and state-law duties could easily have been avoided if the regulated actor had simply ceased acting.

Id. at 488 (quoting *PLIVA*, 564 U.S. at 620). The Court cited *PLIVA* as an obvious example:

> [T]he *PLIVA* Court held that the state failure-to-warn claims were preempted by the FDCA because it was impossible for drug manufacturers to comply with both the state-law duty to label their products in a way that rendered them reasonably safe and the federal-law duty not to change their drugs' labels. It would, of course, have been possible for drug manufacturers like PLIVA to pull their products from the market altogether. In so doing, they would have avoided liability under both state and federal law: such manufacturers would neither have labeled their products in a way that rendered them unsafe nor impermissibly changed any federally approved label.

Id. (citation omitted).

Similarly, in this case, Genentech cannot be forced to stop selling vials that comply with FDA requirements in order to avoid liability under state law claims.

V. Conclusion

For the reasons set forth above, Defendant's Motion for Summary Judgment Based on Federal Preemption (Doc. 201), is hereby granted.

ENTERED this 20th day of March, 2019.

Terence C Kern

TERENCE C. KERN
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OKLAHOMA

IN RE: GENENTECH, INC.,	)	
HERCEPTIN (TRASTUZUMAB)	)	MDL DOCKET NO. 16-MD-2700
MARKETING AND SALES	)	
PRACTICES LITIGATION	)	

JUDGMENT

Pursuant to the Court's Opinion and Order of March 20, 2019 (Doc. 388) granting Defendant Genentech, Inc.'s Amended Motion for Summary Judgment (Doc 201), judgment is hereby entered in favor of Genentech, Inc., and against Plaintiffs.

ENTERED this 20th day of March, 2019.

Terence C Kern

TERENCE C. KERN
United States District Judge

CERTIFICATE OF DIGITAL SUBMISSION

Counsel for Appellants hereby certifies that all required privacy redactions have been made, which complies with the requirements of Federal Rules of Appellate Procedure 25(a)(5).

Counsel also certifies that the hard copies submitted to the Court are exact copies of the ECF filing of July 31, 2019.

Counsel further certifies that the ECF submission was scanned for viruses with the most recent version of a commercial virus scanning program (Vipre software version 11.0.7629 ; Definitions version 76832–7.81805 [July 31, 2019 Vipre engine version 3.9.2671.2 – 3.0), and according to the program, is free of viruses.

Dated: July 31, 2019

/s/ David L. Bryant
David L. Bryant, OBA No. 1262

CERTIFICATE OF SERVICE

I hereby certify that on July 31, 2019, I electronically transmitted the foregoing Appellants' Opening Brief to the Clerk of the Court using the CM/ECF System for filing and transmittal of a Notice of Electronic Filing and service on the ECF registrants listed below.

I further certify that seven printed copies of the Appellants' Opening Brief will be shipped via Federal Express overnight delivery to the Clerk, United States Court of Appeals for the Tenth Circuit, Byron White U.S. Courthouse, 1823 Stout Street, Denver, Colorado, 80257-1823, for delivery to the Court within two (2) business days of the above date.

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