FILED
United States Court of Appeals
Tenth Circuit

May 29, 2020

Christopher M. Wolpert
Clerk of Court

PUBLISH

UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

In re: MDL 2700 Genentech Herceptin (Trastuzumab) Marketing and Sales Practice 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 REGENT FOR THE STATE OF OKLAHOMA; FLORIDA CANCER SPECIALISTS, P.L., a Florida Professional Limited Liability; HEMATOLOGY-ONCOLOGY ASSOCIATES OF CENTRAL NEW YORK, P.C., a New York Professional Corporation; VIRGINIA CANCER INSTITUTE, 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

No. 19-5035

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;

Plaintiffs - Appellants,

v.

GENENTECH, INC., a California Corporation,

Defendant - Appellee,

and

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

Defendants.

AMERICAN MEDICAL ASSOCIATION; OKLAHOMA STATE MEDICAL ASSOCIATION; PUBLIC JUSTICE, P.C.; CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA; PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA; NATIONAL ASSOCIATION OF MANUFACTURERS; BIOTECHNOLOGY INNOVATION ORGANIZATION; PRODUCT

LIABILITY ADVISORY COUNCIL, INC.,

Amici Curiae.

Appeal from the United States District Court
for the Northern District of Oklahoma
(D.C. No. 4:16-MD-02700-TCK-JFJ)

Matthew W.H. Wessler, Gupta Wessler, Washington, DC (David L. Bryant, Amelia A. Fogleman, Steven J. Adams, Adam C. Doverspike, James Wesley Scott Pebsworth, GableGotwals, Tulsa, Oklahoma, attorneys for Appellants Cancer Care Network of South Texas, P.A., 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., Shenandoah Oncology, PC, Tennessee Oncology, PLLC, Texas Oncology, P.A., Tulsa Cancer Institute, PLLC (now known as Oklahoma Cancer Specialists Management Company, LLC), State of Oklahoma ex rel. Board of Regents for the State of Oklahoma, Virginia Cancer Institute Inc., Virginia Oncology Associates, P.C.; James D. Sill, Matthew J. Sill, Kathryn Eidson Griffin, Tara Tabatabaie, Christopher J. Bergin, Simone Fulmer. Fulmer Sill PLC, Oklahoma City, Oklahoma, attorneys for Appellant Comanche County Memorial Hospital; and Janaki Hannah Nair, Elias Meginnes & Seghetti, P.C., Peoria, Illinois, attorneys for Appellant, Oncology-Hematology Associates of Central Illinois, P.C., with him on the briefs), appearing for Appellants.

Alicia J. Donahue, Shook, Hardy & Bacon, L.L.P., San Francisco, California (Paul W. Schmidt, Covington & Burling LLP, New York, New York; James P. Muehlberger, Shook, Hardy & Bacon, L.L.P., Kansas City, Missouri; Emily Ullman, Covington & Burling LLP, Washington, DC; and William W. O'Connor, Hall, Estill, Hardwick, Gable, Golden & Nelson, P.C., Tulsa, Oklahoma, with her on the briefs), appearing for Appellees.

Jack R. Bierig and Catherine M. Masters, Schiff Hardin LLP, Chicago, Illinois, filed a brief for Amici Curiae American Medical Association and Oklahoma State Medical Association.

Leah M. Nicholls, Public Justice, P.C., Washington, DC, filed a brief for Amicus Curiae Public Justice, P.C.

K. Lee Marshall, Bryan Cave Leighton Paisner LLP, San Francisco, California; Timothy J. Hasken and Samuel E. Hofmeier. Bryan Cave Leighton Paisner LLP, St. Louis, Missouri, filed a brief for Amici Curiae Pharmaceutical Research and Manufacturers of America, National Association of Manufacturers, and Biotechnology Innovation Organization.

Daryl Joseffer and Tara S. Morrissey, United States Chamber Litigation Center, Washington, DC; Jeremy M. Bylund, Jeffrey S. Bucholtz, Marisa C. Maleck, and Gabriel Krimm, King & Spalding LLP, Washington, DC, filed a brief for Amicus Curiae Chamber of Commerce of the United States of America.

Galen D. Bellamy, Meghan Frei Berglind, and Eric L. Robertson, Wheeler Trigg O'Donnell LLP, Denver, Colorado, filed a brief for Amicus Curiae Product Liability Advisory Council, Inc.

Before **BRISCOE**, **McHUGH**, and **MORITZ**, Circuit Judges.

BRISCOE, Circuit Judge.

This appeal arises from a group of fourteen diversity cases that were consolidated by the Judicial Panel on Multidistrict Litigation and transferred to the Northern District of Oklahoma. The plaintiffs in all fourteen cases are cancer treatment providers who purchased multi-dose vials of Herceptin, a breast cancer drug, from defendant Genentech, Inc. (Genentech). Plaintiffs alleged that Genentech violated state law by failing to ensure that each vial of Herceptin contained the labeled amount of the active ingredient, and by misstating the drug concentration and volume on the product labeling. After the cases were consolidated, Genentech moved for summary judgment, arguing that plaintiffs' claims were pre-empted by federal law. The district court agreed with Genentech and

granted summary judgment in its favor. Plaintiffs now appeal. Exercising jurisdiction pursuant to 28 U.S.C. § 1291, we reject the district court's conclusion that plaintiffs' claims are pre-empted by federal law, and we consequently reverse its grant of summary judgment in favor of Genentech and remand for further proceedings.

I

Factual background

a) Genentech and Herceptin

Defendant Genentech is a California corporation with its principal place of business in San Francisco, California. Genentech manufactures, markets and distributes a prescription drug with the brand name of Herceptin© (hereinafter Herceptin). Herceptin is a biological product (or biologic) used to treat breast cancer tumors that overexpress the HER2 protein.[1] The overexpression of HER2 causes breast cancer tumors to grow and spread faster. Herceptin targets the HER2 protein and, in doing so, helps to slow or stop the growth of breast cancer tumors.

b) Federal regulation of biologics

Congress, by way of the Public Health Service Act (PHSA), expressly regulates biological products such as Herceptin. 42 U.S.C. § 262. Generally speaking, the PHSA

[1] Biologics "are drugs that are not chemically synthesized but instead are derived from biological sources such as animals and microorganisms." *Genentech, Inc. v. Immunex R.I. Corp.*, 395 F. Supp. 3d 357, 359–60 (D. Del. 2019). Biologics are intended for "the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1).

provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any biological product unless . . . a biologics license . . . is in effect for the biological product" and "each package of the biological product is plainly marked with . . . the proper name of the biological product contained in the package," "the name, address, and applicable license number of the manufacturer of the biological product," and "the expiration date of the biological product." 42 U.S.C. § 262(a)(1). The PHSA directs the Secretary of Health and Human Services to oversee the approval of biologic licenses, outlines the standards for the approval of such licenses, and authorizes the Secretary to "establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses." *Id.* § 262(a)(2)(A). The Secretary has, in turn, delegated that authority to the United States Food and Drug Administration (FDA).

Consequently, a manufacturer of a biologic must file with the FDA a biologics license application (BLA). 21 C.F.R. § 601.2(a). FDA approval of a BLA "constitute[s] a determination that the . . . product meet[s] applicable requirements to ensure . . . safety, purity, and potency." *Id.* § 601.2(d). FDA approval also results in the issuance of a biologics license.

"The Federal Food, Drug, and Cosmetic Act" (FDCA), which applies to prescription drugs, likewise "applies to a biological product subject to regulation under" the PHSA. 42 U.S.C. § 262(j). This includes the FDCA's labeling requirements. *Id.*; *see also id.* § 262(a)(2)(D).

Section 352 of the FDCA, which is entitled "Misbranded drugs and devices," states, in pertinent part, that "[a] drug or device shall be deemed to be misbranded . . . [i]f its labeling is false or misleading in any particular." 21 U.S.C. § 352(a)(1). Section 352 goes on to state, in pertinent part, that a drug or device shall be deemed misbranded "[i]f 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 . . . by regulations prescribed by the Secretary." *Id.* § 352(b).

FDA regulations implemented under the FDCA require, in part, that "[f]or each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release." 21 C.F.R. § 211.165(a). "Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected." *Id.* § 211.165(f). FDA regulations outline in detail how a manufacturer is to test each lot of a biologic product in terms of potency, sterility, purity, and identity. *Id.* §§ 610.10, 610.12, 610.13, 610.14.

FDA regulations also address, in detail, the labeling of prescription drugs, including biologics. In particular, FDA regulations require "[t]he label of a prescription . . . drug in package form" to "bear a declaration of the net quantity of contents." 21 C.F.R. § 201.51(a). "The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package." *Id.* § 201.51(g). "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." *Id.* "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 [(USP)] for filling of ampules." *Id.* "In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight." *Id.* Whether Herceptin constitutes a "liquid drug" or a "solid drug" for purposes of § 201.51(g) is important to the resolution of this case and will be discussed in greater detail below.

c) The production and clinical use of Herceptin

Herceptin is produced from living organisms, namely cells from a Chinese hamster ovary (CHO) cell line that have been genetically modified to produce trastuzumab, the active ingredient. The CHO cells grow and replicate in large bioreactor tanks, with modified cells replicating in a culture medium and producing trastuzumab. The trastuzumab is ultimately harvested from the CHO cells and the resulting protein solution is referred to as the "drug substance." Aplt. App., Vol. 7 at 1367.

The drug substance is tested to ensure that its protein concentration is within the FDA-approved range of 25 milligrams per milliliter (mg/mL), plus or minus 1 mg/mL. If the drug substance protein concentration is outside the approved range, the batch is rejected. If it is within the approved range, the batch is frozen. After being frozen, the

batch is shipped to manufacturing facilities where it is thawed and tested again to ensure that the drug substance protein concentration remains within the FDA-approved range.

At Genentech's manufacturing facilities, the drug substance is filtered, sterilized, and dispensed into glass vials by automated filling machines.[2] The target fill weight for each multi-dose vial is 17.92 grams. The BLA that was filed by Genentech and approved by the FDA allowed for a fill weight range of 17.74 to 18.1 grams, or approximately ± 1%. The FDA subsequently approved greater fill weight ranges for at least some of Genentech's manufacturing facilities.

The vials of drug substance are then lyophilized, i.e., freeze-dried. This process removes most of the water from the substance and leaves what is known as the Herceptin "cake." *Id.* at 1368. The cake is comprised of the dry solid protein and some inactive ingredients. The vials are then sealed.

Because the drug substance protein concentration and fill weight varies to some degree from batch to batch, the result is that the weight of the Herceptin cake in each multi-dose vial also varies to some degree in a range around 440 mg. The FDA-approved

[2] Genentech manufactures Herceptin at three facilities in the United States: South San Francisco (sometimes referred to in the record as the Genentech Parenteral Manufacturing Facility or GPMF); Hillsboro, Oregon (sometimes referred to in the record as Hillsboro Technical Operations or HTO); and Greenville, North Carolina (sometimes referred to in the record as the Dutch State Mines or Patheon facility). The manufacturing process is similar at all three sites. Herceptin is also manufactured internationally.

protein content specification for each multi-dose vial of Herceptin is 440 mg ± 35 mg, resulting in an FDA-approved range of 405 to 475 mg per multi-dose vial.[3]

When a vial of Herceptin is shipped to a health care provider, the Herceptin cake inside of the vial must be reconstituted before the drug can be administered to patients. There are two methods of reconstitution. First, the provider can reconstitute each multi-dose "vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL trastuzumab." *Id.* at 1397. Second, "[i]n patients with known hypersensitivity to benzyl alcohol," a health care provider can "reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution." *Id.*

After the Herceptin cake is reconstituted, the provider calculates the amount of Herceptin solution needed for a specific patient based on the patient's body weight, withdraws the appropriate amount, and injects it into an intravenous bag for delivery. Any Herceptin solution remaining in the vial can be used for up to 28 days to treat additional patients, so long as the Herceptin was reconstituted using a preservative. Otherwise, any remaining Herceptin solution must be immediately discarded.

---

[3] According to Genentech's own internal documents, this range was proposed by Genentech in its BLA, and subsequently approved by the FDA. Aplt. App., Vol. 9 at 2165. Notably, Genentech "simply applied a 'rule of thumb'—an arbitrary rule—to create the range around the target value." *Id.* "The idea was to register as wide a range as possible, and then [Genentech] could make changes within the registered range without notifying the [FDA]." *Id.*

d) *Labeling of and product information for Herceptin*

The BLA submitted by Genentech to the FDA for Herceptin described in detail the "DRUG PRODUCT QUANTITATIVE COMPOSITION" and, in particular, stated that the "Amount [of trastuzumab] per mL" was "25.0 mg" and the "Nominal Amount" of trastuzumab "per Vial" was "440 mg." *Id.*, Vol. 14 at 3322. On that same page, the BLA described the "Vial Configuration" as follows: "Filled to deliver 400 mg trastuzumab per vial." *Id.*

When the FDA approved Genentech's BLA for Herceptin in September 1998, it informed Genentech: "In accordance with approved labeling, your product will bear the tradename Herceptin and will be marketed in 440 mg multi-dose vials supplied with Bacteriostatic Water for Injection, USP (containing 1.1% benzyl alcohol)." *Id.*, Vol. 7 at 1449. Similarly, the FDA-approved Prescribing Information for Herceptin stated that "Herceptin is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum." *Id.* at 1428.

The vial labels and product packaging, as initially approved by the FDA in September 1998, "stated that reconstitution with 20 mL of diluent 'yields a 21 mL multi-dose solution containing 21 mg/mL Trastuzumab.'" *Id.* at 1468. In August 1999, however, the FDA informed Genentech that the FDA had received reports from healthcare providers indicating that they were unable to recover 21 mL of reconstituted Herceptin from each multi-dose vial. *Id.* The FDA further informed Genentech that FDA personnel had similar difficulties with the vials of Herceptin that they tested. *Id.*

The FDA directed Genentech to (a) revise the vial labels and product packaging to remove the reference to "21 mL," and (b) send a letter to its database of Herceptin customers addressing this issue. *Id.*

On September 23, 1999, Genentech, as directed by the FDA, issued to its Herceptin customers a letter that was entitled "IMPORTANT PRESCRIBING INFORMATION." *Id.* at 1534. The letter stated, in pertinent part:

> 4. EXPECTED HERCEPTIN RECOVERY
>
> One multi-dose vial of HERCEPTIN reconstituted with 20 mL of the supplied BWFI diluent contains a solution with an approximate concentration of 21 mg/mL of Trastuzumab. The expected recovery is 20 ± 0.5 mL per vial, and can vary depending on the technique applied and the number of withdrawals from the vial.
>
> * * *
>
> We are working together with the FDA to revise the product labeling accordingly.

Id. The letter thus, in effect, informed healthcare providers that they could expect to recover between 409.5 and 430.5 mg of trastuzumab per multi-dose vial.[4] Other than removing the reference to "21 mL" that appeared on the original packaging, however, Genentech neither proposed to the FDA, nor ultimately made, any other changes to Herceptin's product labeling to more fully convey to its customers the amount of trastuzumab that they could expect to recover from each multi-dose vial of Herceptin.

[4] This range is based on multiplying the fill weight per multi-dose vial, i.e., 20 ± 0.5 mL, times the approximate concentration of 21 mg/mL per multi-dose vial.

Until 2017, multi-dose vials of Herceptin were shipped to healthcare providers in cartons that stated on the front: "Herceptin© trastuzumab 440 mg." *Id.* at 1516. On one side of the cartons was the following:

> **Contents**: Each carton contains one preservative-free 440 mg vial of HERCEPTIN© (Trastuzumab), a recombinant humanized monoclonal antibody, and one vial containing 20 mL of Bacteriostatic Water for Injection, USP (1.1% benzyl alcohol).
>
> The nominal content of each HERCEPTIN vial is 440 mg Trastuzumab, 400 mg α,α–trehalose dihydrate, 9.9 mg L-histidine, and 1.8 mg polysorbate 20. No U.S. standard of potency.

Id. The other side of the cartons included the following information:

> **Reconstitution, Dosage, and Administration**:
>
> Do not use if vacuum is not present. For IV administration only. See enclosed full prescribing information for reconstitution, dilution directions, dosage, and administration. Reconstitute with 20 mL Bacteriostatic Water for Injection (BWFI), USP (1.1% benzyl alcohol) to yield a multi-dose solution containing approximately 21 mg/mL Trastuzumab at a pH of approximately 6.

Id. Nowhere did the carton indicate, as was stated in the BLA, that each vial was designed to deliver only 400 mg of trastuzumab.[5] Nor did the carton indicate, as Genentech did in its September 23, 1999 letter to its customers, that they should expect to be able to retrieve only between 409.5 and 430.5 mg of trastuzumab per vial.

[5] There appears to be no evidence in the record indicating why the product labeling proposed and ultimately used by Genentech did not include information informing healthcare providers that each vial was designed to deliver only 400 mg of trastuzumab. *E.g.*, Aplt. App., Vol. 11 at 2618 (internal Genentech document, dated October 22, 2014, noting that "[t]here [wa]s no documented discussion of 400 mg being included in the labeling.").

Between September 1998 and February 2017, the FDA approved more than ten supplemental applications from Genentech proposing revisions to the Herceptin Prescribing Information. *Id.* at 1370. None of those supplemental applications, however, addressed or altered the labeling description of the product's net weight or concentration. *Id.*

e) *Fill weight data*

The FDA-approved BLA, as noted, listed a target fill weight per vial of Herceptin of 17.92g, with a control limit of ± 0.18g. Assuming a drug substance concentration at the target of 25 mg/mL, Genentech would had to have used a minimum fill weight of 17.776g to guarantee 440 mg of trastuzumab per vial.[6]

The parties dispute whether Genentech, between 1998 and approximately 2017, manipulated the minimum fill weight at its Herceptin manufacturing facilities. Genentech asserts that "[t]he target fill weight at each Herceptin manufacturing site always exceeded the label claim and there is no evidence that [it] was deliberately configuring its equipment or otherwise manipulating its processes to achieve an amount below the target." *Id.*, Vol. 14 at 3261. The available evidence, however, indicates

[6] To calculate the total amount of trastuzumab per vial, the vial fill weight is first divided by the density of Herceptin (1.01 g/mL) to account for the lyophilization of the liquid drug substance. Aplt. App., Vol. 14 at 3356. This results in a "fill volume," which is then multiplied by the drug substance concentration to produce the total amount of trastuzumab for the vial. *Id.*

otherwise. For example, the evidence indicates that in June 2014, the minimum fill weights at all three Herceptin drug manufacturing facilities in the United States were, respectively, 17.74g (South San Francisco), 17.65g (Hillsboro), and 17.56g (Greenville).

If a batch of Herceptin is manufactured with a fill weight of 17.65g (the minimum fill weight at the Hillsboro facility in June 2014) and a drug substance concentration of 25 mg/mL, the resulting drug product will contain less than 437 mg of trastuzumab per vial. If a batch of Herceptin is manufactured with a fill weight of 17.74g (the minimum fill weight at South San Francisco in June 2014) and using a drug substance concentration of 25 mg/mL, the resulting drug product will contain less than 440 mg of trastuzumab per vial.

f) Drug substance concentration data

From 1998 until 2009, the average drug substance concentration per batch of Herceptin was largely above the target of 25 mg/mL. In 2010, however, the average drug substance concentration per batch fell to 24.65 mg/mL. The average drug substance concentration per batch remained below 25 mg/mL until 2015, when it rose to 25.05 mg/mL.

g) Trastuzumab data

In 1998, and in the years between 2000 and 2007, the average amount of trastuzumab per vial of Herceptin distributed in the United States exceeded 440 mg. In 1999, and from 2008 through 2017, however, the average amount of trastuzumab per vial of Herceptin distributed in the United States was less than 440 mg. More specifically, the

average amount of trastuzumab per vial varied from 428.64 mg per vial in 2012 to 439.94 mg per vial in 2008. Thus, the average amount of trastuzumab per vial protein declined by approximately 15 mg per vial between 1998 and 2017.

It was purportedly Genentech's policy not to investigate why batches of Herceptin vials fell below 440 mg of trastuzumab per vial, so long as the amount of trastuzumab per vial fell within the specification range of 405 to 475 mg per vial that was outlined in the BLA. Notwithstanding that purported policy, however, the evidence available in the record on appeal suggests that Genentech maintained a considerable amount of control over its manufacturing processes and, in turn, the amount of trastuzumab per vial. For example, in 2003, Genentech changed the drug substance from version 1.0 to version 1.1. That change led to significantly lower variations in the drug substance concentration per batch and arguably should have led to lower variations in the amount of trastuzumab per vial.

h) *Genentech's handling of customer inquiries regarding Herceptin*

Genentech received "frequent inquiries" from healthcare providers regarding the amount of trastuzumab in Herceptin multi-dose vials. *Id.*, Vol. 11 at 2516. The inquiries focused on the "apparent discrepancy between the nominal 440 mg amount stated on the Herceptin vial [label] vs. the amount [the healthcare providers] calculate[d] that they [could] physically extract" per vial. *Id.* at 2522. In 2002, Genentech "reassur[ed]" one oncology group "that the vial do[es] contain what i[t] says it contains, a

minimum of 440 mg," and that "the amount of Herceptin per vial and corresponding concentrations are stated as minimums." *Id.*, Vol. 8 at 1664; Vol. 13 at 3176, 3179.

Genentech, however, subsequently changed its position on that issue. In 2014, for example, Genentech created a memo (the Q&A Memo) to help Genentech employees answer questions from healthcare providers regarding why they could not obtain the labeled amount from Herceptin vials. According to the Q&A Memo, "[k]ey messages" to be conveyed in response to these inquiries were that "Herceptin is supplied in 440 mg multi-dose vials as a lyophilized powder containing 440 mg trastuzumab," and "Herceptin 440 mg multi-dose vials are labelled according to the amount they contain, not according to the expected extractable amount." *Id.*, Vol. 11 at 2529-30.

i) The FDA's draft and final guidance documents

In March 2014, the FDA published a draft guidance document entitled "Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products" (Draft Guidance). *Id.* at 2477. In a section entitled "Overview," the Draft Guidance stated, in pertinent part:

> The United States Pharmacopeia (USP) General Chapter < 1 > *Injections* provides that each container of an injectable product is filled with a volume that slightly exceeds the content indicated in the labeling. The excess volumes are meant to be sufficient to permit withdrawal and administration of the labeled volumes. FDA regulations at 21 CFR 201.51(g) provide that for drugs in ampules or vials that are intended for injection, the declaration of net quantity of contents on the label is considered to express the minimum quantity of contents and further requires that variation above the stated measure must comply with the excess volumes set forth in USP. USP General Chapter <1151> *Pharmaceutical Dosage Forms* provides excess volume recommendations for mobile and viscous liquids in a range

> of container sizes, noting that the excess volumes recommended are usually sufficient to permit withdrawal and administration of the labeled volumes. * * * Generally, a sponsor should not declare the amount of overfill on the container label.

Id. at 2478 (footnotes omitted). In a subsequent section entitled "DISCUSSION," the Draft Guidance stated, in pertinent part:

> 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). The regulation requires a sponsor/applicant to comply with the excess volume recommendations prescribed by the USP. Specifically, for drugs in ampules and vials, intended for injection, a sponsor/applicant must comply with the excess volume recommendations that appear in USP General Chapter <1151>.

Id. at 2479.

In June 2015, the FDA issued a final version of the Draft Guidance that included the same language. *Id.*, Vol. 5 at 1110. The only relevant changes from the Draft Guidance were the alteration of the heading "DISCUSSION" to "DISCUSSION AND RECOMMENDATIONS," and the addition of the following sentence to the "DISCUSSION AND RECOMMENDATIONS" section: "*In the case of drug products requiring reconstitution, the product should be designed to meet the label claim and acceptable overfill, and allow for correct dosing.*" *Id.* at 1115 (emphasis added).

j) Communications between FDA and Genentech regarding vial volume

At some point in 2014, the FDA received complaints from an unidentified oncology pharmacy specialist and other oncology institutions regarding the inability of providers to withdraw 21 mL volume from each vial of Herceptin. On October 30, 2014,

FDA and Genentech held a teleconference to discuss whether the Herceptin vials should be labeled based on the amount of trastuzumab that they contained or the amount of trastuzumab that could be removed from the vials and administered to patients. The FDA noted "that the original BLA submission state[d] that the vial contain[ed] 440 mg of trastuzumab, but after reconstitution, the vial allow[ed] for recovery of '400 mg of HERCEPTIN drug product.'" *Id.*, Vol. 7 at 1530. The FDA in turn "asked for justification of the discrepancy between the label claim and recoverable amount as initially provided in the BLA and stated that the label should reflect the amount of recoverable product in the vial once reconstituted." *Id.* Genentech told the FDA that Herceptin vials were labeled to contain the target fill amount and not the deliverable amount.

Genentech's internal communications, however, suggest that there was confusion among Genentech personnel regarding how 21 C.F.R. § 201.51(g) applied to Herceptin and, in turn, whether "the label claim should be deliverable amount [or] contained amount." *Id.*, Vol. 11 at 2647. One such communication noted, for example, that there were other "multi-dose vials, lyophilized powders for injection" on the market "that specif[ied] the 'to deliver' amount." *Id.* at 2638. Some Genentech employees believed that Genentech was not properly following § 201.51(g)'s labeling requirements. *E.g.*, *id.* at 2647 ("My interpretation was the label claim should be deliverable amount not contained amount.").

The FDA informed Genentech that it "did not agree that the Herceptin label complies with 21 CFR [§] 201.51(g) based on the Agency's current thinking as reflected in the Draft Guidance on Labeled Vial Fill Size issued by the Agency earlier this year." *Id.*, Vol. 14 at 3268. The FDA further stated that "under the new draft guidance for Industry, the vial label should be revised to reflect the maximum amount of product that can be removed from the vial and that the label cannot claim more than can be extracted." *Id.*

On December 5, 2014, Genentech sent the FDA a written response proposing the addition of language to the Herceptin label stating that recovery of Herceptin may be lower when the 440 mg vial is used as a multi-dose vial.

On February 3, 2017, the FDA sent Genentech a "GENERAL ADVICE" letter disagreeing with Genentech's proposed labeling changes and directing Genentech to submit a plan to address revision of the labeling from 440 mg per vial to 420 mg per vial and to prepare a communication plan to educate healthcare practitioners on the labeling change. *Id.*, Vol. 7 at 1578. The FDA noted in the letter that "the original BLA stated that Herceptin drug product vials are 'filled to deliver 400 mg trastuzumab.'" *Id.* The FDA in turn noted that Genentech's "proposed edits to the prescribing information . . . w[ould] not enable the recovery of 440 mg of Herceptin after reconstitution." *Id.* Consequently, the FDA "recommend[ed] that the labeling for Herceptin be revised to 420 mg based upon the recovery of 20 mL of the 21 mg/mL reconstituted solution." *Id.*

According to Genentech's own internal documents, FDA officials were "very clear on their expectation that each vial" of Herceptin should contain sufficient drug product, "post reconstitution[,] to be consistent with [the] label claim." *Id.*, Vol. 13 at 3095; *see also id.* at 3098, 3103, 3108. The FDA also informed Genentech that the FDA had "not changed anything in [its] guidance and [Genentech] should have known to make this change all along." *Id.*, Vol. 9 at 2114. Genentech, on the other hand, "view[ed] th[e] new requirement as a change in [the FDA's] guidance that was not obvious, even in the most recent Guidance issued in 2015." *Id.*

k) *Genentech's change to 150 mg single-dose vials*

Ultimately, Genentech never produced or distributed any multi-dose vials of Herceptin labeled to contain 420 mg of trastuzumab. Instead, Genentech ceased production of Herceptin 440 mg multi-dose vials in 2017. It then switched to single-dose Herceptin vials labeled "150 mg." *Id.*, Vol. 9 at 2124. Although the FDA approved a protein content specification range for the 150 mg vial of 150 to 176 mg, the FDA requires Genentech to put no less than 156 mg of trastuzumab in each vial to ensure that healthcare providers can withdraw the labeled amount.

Procedural background

The plaintiffs in these fourteen consolidated diversity actions are cancer treatment providers who have purchased Herceptin for treatment of their patients. Plaintiffs filed these actions in various districts throughout the country challenging the labeling of Herceptin. Plaintiffs alleged in their respective complaints that, despite the labels on

multi-dose vials of Herceptin stating that each vial contains 440 mg of Herceptin at a concentration of 21 mg/mL, in actuality every vial "is never more than 20.2 mL." *Id.*, Vol. 2 at 411. Plaintiffs further alleged in their complaints that "[t]his shortage [wa]s caused either by a lower amount of Herceptin being provided than advertised or a higher concentration of Herceptin after mixing than advertised." *Id.* "Regardless [of] the cause of the discrepancy," plaintiffs alleged that they "d[id] not receive 20.952 mL of fluid solution after following Genentech's direction despite paying for the 20.952 mL quantity." *Id.* at 412. "Either way," the complaints alleged, plaintiffs were "forced to purchase additional Herceptin because following Genentech's Preparation of Administration instructions yield[ed] less volume of fluid solution than mathematically follow[ed] from Genentech's representation and warranties." *Id.* at 416.

Each of the complaints asserted claims under state law for breach of express and implied warranties and unjust enrichment. The express warranty claims alleged, in particular, that Genentech falsely represented and warranted that "[e]ach vial purchased . . . contain[ed] 440 mg of Herceptin," "[e]ach reconstituted vial of Herceptin yield[ed] fluid solution with a density of 21 mg/mL," and "[e]ach reconstituted vial of Herceptin contain[ed] 20.952 mL of fluid solution." *Id.* at 417. The complaints sought actual damages ("damages suffered through the date of judgment as a result of Genentech's activities and conduct"), costs, and attorneys' fees. *Id.* at 418.

The Judicial Panel of Multidistrict Litigation consolidated the cases into this multidistrict litigation. Plaintiffs in two cases sought certification of a nationwide class.

On April 24, 2017, Genentech moved for summary judgment, arguing that plaintiffs' claims were, for two separate reasons, pre-empted by federal law. First, Genentech argued that plaintiffs' state-law claims posed an obstacle to the federal regulatory scheme for prescription drugs and biologics because that scheme allows for reasonable variations in manufacturing and labeling. Second, Genentech argued that plaintiffs' claims were also pre-empted because, if successful, they would make it impossible for Genentech to comply with both state and federal law requirements in terms of its manufacturing and labeling of Herceptin.

Plaintiffs argued in their response that imposing state-law liability on Genentech for underfilling Herceptin vials did not present an obstacle to a congressional purpose. In support, plaintiffs asserted that federal law precludes Genentech from systemically underfilling Herceptin vials. Plaintiffs further asserted that their state-law claims essentially "mirror[ed] federal misbranding law" applicable to prescription drugs and biologics. *Id.*, Vol. 8 at 1688.

Plaintiffs also argued that, even if their state law claims sought to impose a standard more stringent than that imposed by federal law, their claims did not pose an obstacle to a congressional purpose. Plaintiffs argued in support that the Supreme Court has rejected the notion "that any state law imposing standards in an area subject to federal drug regulation that are different or higher than the federal standard poses an obstacle to that regulatory scheme and should be preempted." *Id.* at 1690 (citing *Wyeth v. Levine*, 555 U.S. 555 (2009)). Plaintiffs further argued that the FDCA does not contain an

express pre-emption provision, and that Genentech could not establish that the state law claims stood as an obstacle to the achievement of congressional objectives.

On March 20, 2019, the district court issued a written opinion and order granting summary judgment in favor of Genentech. With respect to the issue of obstacle pre-emption, the district court agreed with Genentech that plaintiffs' claims were "barred because they impose[d] an obstacle to the FDA's 'reasonable variations' determination and [we]re inconsistent with federal law." *Id.*, Vol. 6 at 1328. In reaching this conclusion, the district court noted that the FDA's "net quantity labeling regulation[]," 21 C.F.R. § 201.51(g), "distinguish[es] between liquid and solid drugs." *Id.* at 1330. The district court in turn concluded that "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." *Id.* Thus, the district court concluded that "[p]laintiffs' labeling claims conflict[ed] with federal law, which permits reasonable variations for solid drugs sold in vials." *Id.* In addition, the district court rejected plaintiffs' argument "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.'" *Id.* at 1331. "The undisputed facts," the district court noted, "establish[ed] that the FDA has always treated Herceptin as a solid drug, and has allowed reasonable variations as provided in the USP." *Id.* at 1334. The district court further concluded that, because "USP General Chapter <905>, *Uniformity of Dosage Units*, provides for an allowable variation of 15% around the label claim," plaintiffs'

"'concentration' and 'solution volume' claims" were also barred by obstacle pre-emption. *Id.*

The district court also agreed with Genentech that plaintiffs' claims were barred by the doctrine of impossibility pre-emption. The district court stated "[i]t [wa]s 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." *Id.* at 1335. "Changing the target fill weight," the district court noted, "which is an in-process specification identified in the BLA, requires prior FDA approval." *Id.* Likewise, the district court noted, "chang[ing] from the originally approved static filling process to a variable filling method to ensure 440 mg per vial" would also "require prior FDA approval because the manufacture of Herceptin is an aseptic (sterile) processing operation." *Id.* at 1336. Lastly, the district court noted that "[c]hanging the concentration stated on the label . . . would [also] require FDA approval."[7] *Id.*

The district court entered final judgment in the case on March 20, 2019. Plaintiffs filed a notice of appeal on April 18, 2019.

[7] The district court also rejected plaintiffs' argument "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." Aplt. App., Vol. 6 at 1336. Because we reject Genentech's other grounds for pre-emption, it is unnecessary for us to reach this issue.

II

In their appeal, plaintiffs challenge the district court's grant of summary judgment in favor of Genentech. More specifically, plaintiffs challenge the district court's conclusions that the doctrines of obstacle pre-emption and impossibility pre-emption both bar plaintiffs' claims. As discussed below, we agree with plaintiffs that neither obstacle nor impossibility pre-emption applies in this case, and we therefore reverse the district court's grant of summary judgment in favor of Genentech and remand for further proceedings on plaintiffs' claims.

Standard of review

"We review a district court's grant of summary judgment de novo." *Arlin Geophysical Co. v. United States*, 946 F.3d 1234, 1237 (10th Cir. 2020). "A party is entitled to summary judgment if 'there is no genuine dispute as to any material fact.'" *Id.* (quoting Fed. R. Civ. P. 56(a)).

In conducting this analysis, "we engage in de novo review of all the district court's legal conclusions." *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1095 (10th Cir. 2017). "Thus, we ordinarily consider pre[-]emption as a legal issue subject to de novo review." *Id.* at 1096.

Pre-emption principles

"The Supremacy Clause establishes that federal law 'shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.'" *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 617 (2011) (quoting U.S.

Const., Art. VI, cl. 2). Supreme Court precedent "establishe[s] that state law is pre-empted under the Supremacy Clause . . . in three circumstances." *English v. Gen. Elec. Co.*, 496 U.S. 72, 78 (1990). "First, Congress can define explicitly the extent to which its enactments pre-empt state law." *Id.* "Pre-emption fundamentally is a question of congressional intent, and when Congress has made its intent known through explicit statutory language, the courts' task is an easy one." *Id.* at 78–79 (citation omitted). "Second, in the absence of explicit statutory language, state law is pre-empted where it regulates conduct in a field that Congress intended the Federal Government to occupy exclusively." *Id.* at 79. "Finally, state law is pre-empted to the extent that it actually conflicts with federal law." *Id.* "Thus," the Supreme Court "has found-pre-emption where it is impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.* (quotations and citation omitted).

The Supreme Court has identified "two cornerstones" that must guide a court's pre-emption analysis. "First, 'the purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Wyeth*, 555 U.S. at 565 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). "Second, [i]n all pre-emption cases, and particularly in those in which Congress has legislated . . . in a field which the States have traditionally occupied, . . . [a court] start[s] 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." *Id.* (quotations omitted).

In this case, it is undisputed that Congress did not include an express pre-emption provision in either the PHSA or the FDCA.[8] Further, there is no assertion by Genentech, nor any evidence otherwise, that Congress intended the federal government to exclusively occupy the field of prescription drugs in general, or biologics in particular. That leaves only the third category of pre-emption, which includes both obstacle and impossibility pre-emption. Genentech argued in its summary judgment motion, and the district court ultimately agreed, that both obstacle and impossibility pre-emption applied to plaintiffs' claims. As we shall proceed to discuss, we conclude that Genentech has failed to establish that either of these doctrines apply to plaintiffs' claims.

The Supreme Court's decision in Wyeth

Before turning to plaintiffs' challenges to the district court's pre-emption rulings, it is useful to first review, in some detail, the Supreme Court's decision in *Wyeth*. Although the claims at issue in *Wyeth* were not identical to those alleged by the plaintiffs in these cases, the cases bear enough similarities that much of the discussion in *Wyeth*, particularly the discussion of the history of federal regulation of drug labeling, is useful for purposes of the analysis in this case. Moreover, plaintiffs rely heavily on *Wyeth* in

[8] Neither the PHSA nor the FDCA contains a provision expressly preempting states from regulating biologics. Further, "[t]he 1962 amendments" to the FDCA "added a saving clause, indicating 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.

asserting that their state law claims do not impose an obstacle to the federal regulatory scheme for prescription drugs.

The plaintiff in *Wyeth*, Diane Levine, was injured from an IV-push injection of the drug Phenergan. Phenergan, which is manufactured and distributed by defendant Wyeth, is "an antihistamine used to treat nausea." 555 U.S. at 559. It "can be administered intramuscularly or intravenously, and it can be administered intravenously through either the 'IV-push' method, whereby the drug is injected directly into a patient's vein, or the 'IV-drip' method, whereby the drug is introduced into a saline solution in a hanging intravenous bag and slowly descends through a catheter inserted in a patient's vein." *Id.* "The drug is corrosive and causes irreversible gangrene if it enters a patient's artery." *Id.* On April 7, 2000, Levine twice visited a local clinic "for treatment of a migraine headache" and "nausea." During the second visit, a physician assistant administered Phenergan "by the IV-push method, and Phenergan entered Levine's artery, . . . where it came in contact with arterial blood." *Id.* "As a result, Levine developed gangrene, and doctors amputated first her right hand and then her entire forearm." *Id.* Levine settled claims with the clinic and physician assistant, and then filed suit against Wyeth, "relying on common-law negligence and strict-liability theories." *Id.* "Although Phenergan's labeling warned of the danger of gangrene and amputation following inadvertent intra-arterial injection, Levine alleged that the labeling was defective because it failed to instruct clinicians to use the IV-drip method of intravenous administration instead of the higher risk IV-push method." *Id.* at 559–60 (footnote omitted).

"Wyeth filed a motion for summary judgment, arguing that Levine's failure-to-warn claims were pre-empted by federal law." *Id.* at 560. The trial court denied Wyeth's motion, finding "no merit in either Wyeth's field pre-emption argument . . . or its conflict pre-emption argument." *Id.* The case proceeded to a jury trial. "[T]he trial judge instructed the jury that it could consider evidence of Wyeth's compliance with FDA requirements but that such compliance did not establish that the warnings were adequate." *Id.* at 562. "Answering questions on a special verdict form, the jury found that Wyeth was negligent, that Phenergan was a defective product as a result of inadequate warnings and instructions, and that no intervening cause had broken the causal connection between the product defects and the plaintiff's injury." *Id.* "It awarded total damages of $7,400,000, which the court reduced to account for Levine's earlier settlement with the health center and clinician." *Id.* After trial, the court denied Wyeth's motion for JMOL.

The Vermont Supreme Court later affirmed. But the chief justice of that court dissented, arguing "that the jury's verdict conflicted with federal law because it was inconsistent with the FDA's conclusion that intravenous administration of Phenergan was safe and effective." *Id.* at 563. The United States Supreme Court then granted certiorari due to "[t]he importance of the pre-emption issue, coupled with the fact that the FDA ha[d] changed its position on state tort law and . . . endorse[d] the views expressed" by the chief justice of the Vermont Supreme Court in his dissent. *Id.*

Before the Supreme Court, Wyeth "ma[de] two separate pre-emption arguments." *Id.* First, Wyeth argued "that it would have been impossible for it to comply with the state-law duty to modify Phenergan's labeling without violating federal law." *Id.* Second, Wyeth argued "that recognition of Levine's state tort action create[d] an unacceptable obstacle to the accomplishment and execution of the full purposes and objectives of Congress because it substitute[d] a lay jury's decision about drug labeling for the expert judgment of the FDA." *Id.* at 563–64 (quotations and citation omitted). The Supreme Court concluded that "[t]he narrow[] question presented [wa]s whether federal law pre-empts Levine's claim that Phenergan's label did not contain an adequate warning about using the IV-push method of administration." *Id.* at 565.

In addressing that question, the Court began by "briefly review[ing] the history of federal regulation of drugs and drug labeling." *Id.* at 566. It noted:

> In 1906, Congress enacted its first significant public health law, the Federal Food and Drugs Act, ch. 3915, 34 Stat. 768. The Act, which prohibited the manufacture or interstate shipment of adulterated or misbranded drugs, supplemented the protection for consumers already provided by state regulation and common-law liability. In the 1930's, Congress became increasingly concerned about unsafe drugs and fraudulent marketing, and it enacted the Federal Food, Drug, and Cosmetic Act (FDCA), ch. 675, 52 Stat. 1040, as amended, 21 U.S.C. § 301 *et seq*. The FDCA's most substantial innovation was its provision for premarket approval of new drugs. It required every manufacturer to submit a new drug application, including reports of investigations and specimens of proposed labeling, to the FDA for review. Until its application became effective, a manufacturer was prohibited from distributing a drug. The FDA could reject an application if it determined that the drug was not safe for use as labeled, though if the agency failed to act, an application became effective 60 days after the filing. FDCA, § 505(c), 52 Stat. 1052.

> In 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer. Before 1962, the agency had to prove harm to keep a drug out of the market, but the amendments required the manufacturer to demonstrate that its drug was "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" before it could distribute the drug. §§ 102(c), 104(b), 76 Stat. 781, 784. In addition, the amendments required the manufacturer to prove the drug's effectiveness by introducing "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." § 102(c), *id.*, at 781.
>
> As it enlarged the FDA's powers to "protect the public health" and "assure the safety, effectiveness, and reliability of drugs," *id.*, at 780, Congress took care to preserve state law. The 1962 amendments added a saving clause, indicating that a provision of state law would only be invalidated upon a "direct and positive conflict" with the FDCA. § 202, *id.*, at 793. Consistent with that provision, state common-law suits "continued unabated despite . . . FDA regulation." *Riegel v. Medtronic, Inc.*, 552 U.S. 310, 340, 128 S. Ct. 999, 1017, 169 L. Ed.2d 892 (2008) (GINSBURG, J., dissenting); see *ibid.*, n. 11 (collecting state cases). And when Congress enacted an express pre-emption provision for medical devices in 1976, *see* § 2, 90 Stat. 574 (codified at 21 U.S.C. § 360k(a)), it declined to enact such a provision for prescription drugs.
>
> In 2007, after Levine's injury and lawsuit, Congress again amended the FDCA. 121 Stat. 823. For the first time, it granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval. § 901(a), *id.*, at 924–926. In doing so, however, Congress did not enact a provision in the Senate bill that would have required the FDA to preapprove all changes to drug labels. See S. 1082, 110th Cong., 1st Sess., § 208, pp. 107–114 (2007) (as passed) (proposing new § 506D). Instead, it adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels. See 121 Stat. 925–926.

Id. at 566–68.

Turning to Wyeth's pre-emption arguments, the Court first rejected Wyeth's argument "that Levine's state-law claims [we]re pre-empted because it [wa]s impossible

for it to comply with both the state-law duties underlying those claims and its federal labeling duties." *Id.* at 568. In doing so, the Court noted there was "an FDA regulation that permit[ted] a manufacturer to make certain changes to its label before receiving the [FDA's] approval," and that, "[a]mong other things, this 'changes being affected' (CBE) regulation provide[d] that if a manufacturer [wa]s changing a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction' or to 'add or strengthen an instruction about dosage and administration that [wa]s intended to increase the safe use of the drug product,' it m[ight] make the labeling change upon filing its supplemental application with the FDA" and "it need not wait for FDA approval." *Id.* The Court concluded, based upon the evidence in the record, that "as amputations [associated with Phenergan] continued to occur, Wyeth could have analyzed the accumulating data and added a stronger warning about IV-push administration of the drug." *Id.* at 570. The Court also rejected Wyeth's "suggest[ion] that the FDA, rather than the manufacturer, bears primarily responsibility for drug labeling." *Id.* at 570. To the contrary, the Court concluded, it was a "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times," meaning that the manufacturer "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 570–71. "Thus," the Court concluded, "when the risk of gangrene from IV-push injection of Phenergan became apparent, Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the

FDA's approval." *Id.* at 571. And, the Court noted, "absent clear evidence that the FDA would not have approved a change to Phenergan's label, [it] w[ould] not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.* The Court therefore rejected Wyeth's impossibility pre-emption arguments. *Id.* at 573.

The Court then turned to Wyeth's argument "that requiring it to comply with a state-law duty to provide a stronger warning about IV-push administration would obstruct the purposes and objectives of federal drug labeling regulation." *Id.* "Levine's tort claims," Wyeth argued, "[we]re pre-empted because they interfere[d] with Congress's purpose to entrust an expert agency to make drug labeling decisions that str[uck] a balance between competing objectives." *Id.* The Supreme Court, however, "f[ou]nd no merit in this argument," noting that the argument "relie[d] on an untenable interpretation of congressional intent and an overbroad view of an agency's power to pre-empt state law." *Id.*

The Court offered the following explanation:

> Building on its 1906 Act, Congress enacted the FDCA to bolster consumer protection against harmful products. *See Kordel v. United States*, 335 U.S. 345, 349, 69 S. Ct. 106, 93 L. Ed. 52 (1948); *United States v. Sullivan*, 332 U.S. 689, 696, 68 S. Ct. 331, 92 L. Ed. 297 (1948). Congress did not provide a federal remedy for consumers harmed by unsafe or ineffective drugs in the 1938 statute or in any subsequent amendment. Evidently, it determined that widely available state rights of action provided appropriate relief for injured consumers. It may also have recognized that state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings.
>
> If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point

> during the FDCA's 70–year history. But despite its 1976 enactment of an express pre-emption provision for medical devices, *see* § 2, 90 Stat. 574 (codified at 21 U.S.C. § 360k(a)), Congress has not enacted such a provision for prescription drugs. *See Riegel*, 552 U.S., at 327, 128 S. Ct., at 1009 ("Congress could have applied the pre-emption clause to the entire FDCA. It did not do so, but instead wrote a pre-emption clause that applies only to medical devices"). Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness. As Justice O'Connor explained in her opinion for a unanimous Court: "The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there [is] between them." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–167, 109 S. Ct. 971, 103 L. Ed.2d 118 (1989) (internal quotation marks omitted); *see also supra*, at 1194 (discussing the presumption against pre-emption).

Id. at 574–75 (footnotes omitted).

Further, the Court rejected Wyeth's reliance on "the preamble to a 2006 FDA regulation governing the content and format of prescription drug labels" in which "the FDA declared that the FDCA establishe[d] both a floor and a ceiling, so that FDA approval of labeling . . . preempt[ed] conflicting or contrary State law." *Id.* at 575 (quotations omitted). In doing so, the Court noted that it never "defer[s] to an agency's *conclusion* that state law is pre-empted," but rather "attend[s] to an agency's explanation of how state law affects the regulatory scheme." *Id.* at 576. In turn, the Court noted, "[t]he weight [it] accord[s] the agency's explanation of state law's impact on the federal scheme depends on its thoroughness, consistency, and persuasiveness." *Id.* at 577. "Under this standard," the Court concluded that "the FDA's 2006 preamble d[id] not

merit deference." *Id.* To begin with, the Court noted, the FDA procedurally erred in finalizing the 2006 regulation because it failed to "offer[] States or other interested parties notice or opportunity for comment" on its "sweeping position on the FDCA's pre-emptive effect in the regulatory preamble." *Id.* Further, the Court concluded, "the preamble [wa]s at odds with what evidence [it had] of Congress' purposes, and it reverse[d] the FDA's own longstanding position without providing a reasoned explanation, including any discussion of how state law has interfered with the FDA's regulation of drug labeling during decades of coexistence." *Id.* The Court noted:

> In keeping with Congress' decision not to pre-empt common-law tort suits, it appears that the FDA traditionally regarded state law as a complementary form of drug regulation. The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge. State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation. The agency's 2006 preamble represents a dramatic change in position.

Id. at 578–79 (footnotes omitted).

Ultimately, the Court "conclude[d] that it [wa]s not impossible for Wyeth to comply with its state- and federal-law obligations and that Levine's common-law claims d[id] not stand as an obstacle to the accomplishment of Congress' purposes in the FDCA." *Id.* at 581.

Obstacle pre-emption

"Congressional enactments that do not exclude all state legislation in [the] same field nevertheless override state laws with which they conflict." *Jones v. Rath Packing Co.*, 430 U.S. 519, 525–26 (1977). This is generally referred to as obstacle pre-emption. Obstacle pre-emption exists when the challenged state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 373 (2000) (quotations omitted), or "to the accomplishment of a significant federal regulatory objective." *Williamson v. Mazda Motor of Am., Inc.*, 562 U.S. 323, 330 (2011). In deciding whether obstacle pre-emption applies in a given case, a court must "consider the relationship between state and federal laws as they are interpreted and applied, not merely as they are written." *Jones*, 430 U.S. at 526.

The district court in this case concluded that plaintiffs' state law claims stood as an obstacle to federal law, in particular the FDA's declaration of net quantity of contents regulation, 21 C.F.R. § 201.51(g). Plaintiffs argue in their appeal that the district court's obstacle pre-emption analysis was flawed for a number of reasons. As we shall proceed to discuss, we generally agree with plaintiffs.

To begin with, plaintiffs argue that the district court "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.'" Aplt. Br. at 27 (quoting Aplt.

App., Vol. 6 at 1331) (emphasis added by plaintiffs). Plaintiffs assert that "[a] drug manufacturer's ability to unilaterally change its label was crucial to the *Wyeth* court's decision regarding ***impossibility*** preemption," but "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." *Id.* Thus, plaintiffs argue, "[t]he district court's effort to distinguish *Wyeth* fails." *Id.*

This argument is correct as far as it goes. Plaintiffs are correct that the Supreme Court rejected defendant Wyeth's impossibility pre-emption defense, and not its obstacle pre-emption defense, on the grounds that federal regulations "permitted Wyeth to unilaterally strengthen its [product] warning." 555 U.S. at 573. Thus, the district court erred in distinguishing *Wyeth* on this basis. But that still leaves the question of whether plaintiffs' state-law suits in this case pose an obstacle to the objectives of Congress, as expressed in the PHSA and the FDCA. *See id.* at 574.

Plaintiffs next argue, again relying on *Wyeth*, that "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." Aplt. Br. at 26. They further argue that "*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." *Id.* (quotations and brackets omitted).

We agree with plaintiffs on this point. Nothing in the federal regulatory scheme required the FDA to ensure that Genentech's proposed label for Herceptin fully complied with all of the statements contained in the BLA. Further, nothing in the federal regulatory scheme required the FDA to police Genentech's distribution practices and ensure that the amount of Herceptin per vial complied with the product label or with federal regulations. Instead, under the FDCA, the FDA establishes general labeling standards, but does not appear to routinely police manufacturers afterwards to ensure that they are fully complying with those standards. Thus, that leaves room for states to impose their own requirements, so long as those requirements do not conflict with the federal regulatory scheme.

Plaintiffs in turn argue, in pertinent part, that "the claims in this case d[id] not eliminate or abridge any goal that the federal regulation seeks to promote." Aplt. Br. at 24. Indeed, they argue that the "basic premise" underlying the district court's obstacle pre-emption analysis "was wrong: federal law does not permit the underfill challenged by Plaintiffs." *Id.* at 36 (emphasis omitted). Instead, plaintiffs argue, "[t]he regulation," i.e., 21 C.F.R. § 201.51(g), "and Herceptin's regulatory history undermine, rather than support, the case for [obstacle] pre[-]emption." *Id.*

To address these arguments, we begin by briefly revisiting the decision in *Wyeth*. The manufacturer in that case, in defending on the grounds of obstacle pre-emption, "contend[ed] that the FDCA establishes both a floor and a ceiling for drug regulation: Once the FDA has approved a drug's label, a state-law verdict may not deem the label

inadequate, regardless of whether there is any evidence that the FDA has considered the stronger warning at issue." *Id.* at 573–74. The Supreme Court rejected this argument, noting "that all evidence of Congress' purposes is to the contrary." *Id.* at 574. The Court explained that "Congress enacted the FDCA to bolster consumer protection against harmful products." *Id.* The Court also noted that "Congress did not provide a federal remedy for consumers harmed by unsafe or ineffective drugs in the 1938 statute or in any subsequent amendment," and therefore "[e]vidently . . . determined that widely available state rights of action provided appropriate relief for injured consumers." *Id.* Further, the Court stated that "[i]f Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history." *Id.* Congress's "silence on the issue," the Court concluded, "coupled with its certain awareness of the prevalence of state tort litigation, [wa]s powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 575. In addition, the Court noted, "the FDA traditionally regarded state law as a complementary form of drug regulation." *Id.* at 578. More specifically, the Court noted, "[s]tate tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly." *Id.* at 579.

Turning to the case at hand, it remains true, as was the situation in *Wyeth*, that "Congress has repeatedly declined to pre-empt state law" in the FDCA. *Id.* at 581. That said, in contrast to the situation in *Wyeth*, where the Court acknowledged the prevalence

of state tort litigation involving prescription drugs, it is unclear from the record whether there is also prevalent state litigation in the area at hand. Specifically, it is unclear from the record how prevalent state litigation is alleging prescription drug manufacturers' breaches of warranties arising from statements made on a product label, particularly claims concerning drug quantity or weight. Thus, it is unclear whether Congress was aware of this possibility and, in turn, whether Congress knowingly decided not to pre-empt such litigation.

We are therefore left to review the substance of federal law, both statutory and regulatory, and compare that to the state law relied on by plaintiffs in order to determine whether there is a conflict. As previously discussed, the production and marketing of biologics is governed by both the PHSA and the FDCA. "Because of the complexity of manufacturing and characterizing a biologic, the [PHSA] emphasizes the importance of appropriate manufacturing control for [such] products." Frequently Asked Questions About Therapeutic Biological Products, https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products (visited on Mar. 18, 2020). The labeling of biologics, however, is not unique in comparison to other prescription drugs and thus is governed by the FDCA and the regulations promulgated by the FDA under the FDCA.

Section 352 of the FDCA, entitled "Misbranded drugs and devices," states, in pertinent part, that a drug shall be deemed misbranded "[i]f 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 . . . by regulations prescribed by the Secretary*." 21 U.S.C. § 352(b) (emphasis added).

The FDA has, consistent with the directive in § 352, implemented regulations that address the labeling of prescription drugs, including biologics such as Herceptin. The key regulation, for purposes of our obstacle pre-emption analysis, is entitled "Declaration of net quantity of contents," and requires "[t]he label of a prescription . . . drug in package form" to "bear a declaration of the net quantity of contents." 21 C.F.R. § 201.51(a). Subsection (g) of this regulation 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.

Id. § 201.51(g).

Because § 201.51(g)'s labeling requirements differ for "liquid drug[s]" and "solid drug[s]," we must, as part of our obstacle pre-emption analysis, determine whether Herceptin constitutes a "liquid drug" or a "solid drug" for purposes of § 201.51(g). In *Kisor v. Wilkie*, 139 S. Ct. 2400 (2019), the Supreme Court recently revisited the

standards that courts must apply in construing agency regulations. "First and foremost," the Court held, "a court should not afford *Auer* deference" to an agency's interpretation of a regulation "unless the regulation is genuinely ambiguous." 139 S. Ct. at 2415 (referring to *Auer v. Robbins*, 519 U.S. 452 (1997)). "If uncertainty does not exist, there is no plausible reason for deference. The regulation then just means what it means—and the court must give it effect, as the court would any law." *Id.* "And before concluding that a rule is genuinely ambiguous, a court must exhaust all the 'traditional tools' of construction." *Id.* "[O]nly when that legal toolkit is empty and the interpretive question still has no single right answer," the Court held, "can a judge conclude that it is 'more [one] of policy than of law,'" and thus look to see, and generally defer to, how the agency has interpreted the regulation.[9] *Id.* (citing *Pauley v. BethEnergy Mines, Inc*., 501 U.S. 680, 696 (1991)).

As noted, § 201.51(g) first refers to "a liquid drug in ampules or vials." The term "liquid" is commonly defined, in its adjective form, to mean "a material substance in that condition (familiar as the normal condition of water, oil, alcohol, etc.) in which its

[9] The district court in this case, in conducting its obstacle pre-emption analysis, concluded that Herceptin was a "solid drug" for purposes of § 201.51(g). But, as best we can determine, it conducted no analysis of the regulatory language in arriving at this conclusion. Instead, the district court looked only to the FDA's approval of the original label proposed by Genentech, the FDA's approval of a 2017 label update, and the USP's definition of the phrase "for injection." Aplt. App., Vol. 6 at 1331. None of this evidence, however, was relevant to the interpretation of § 201.51(g). Further, the district court offered no explanation as to why it afforded no weight or deference to the FDA's 2017 interpretation of Herceptin as a "liquid drug" for purposes of § 201.51(g).

particles move freely over each other (so that its masses have no determinate shape), but do not tend to separate as do those of a gas; not solid nor gaseous." Oxford English Dictionary Online, https://www.oed.com/view/Entry/108914?redirectedFrom=liquid#eid (last visited Mar. 21, 2020). Section 201.51(g) in turn refers to "a solid drug in ampules or vials." The term "solid" is commonly defined, in its adjective form as applied to "material substances," to mean: "Of a dense or massive consistency; composed of particles which are firmly and continuously coherent; hard and compact." *Id.*, https://www.oed.com/view/Entry/184230?rskey=6EAVd5&result=3&isAdvanced=false#eid (last visited on Mar. 21, 2020). These definitions, however, do not necessarily resolve the question before us because Herceptin could, at least arguably, qualify as either a "solid drug" or a "liquid drug," depending upon the point in time that we consider its state. More specifically, Herceptin is shipped to healthcare providers as a freeze-dried block or potential "solid drug." But, before it can be administered to patients, Herceptin must be reconstituted by a healthcare provider, using a vial of bacteriostatic water that is provided by Genentech. Thus, at the time Herceptin is actually administered to a patient, it is clearly a "liquid drug."

To resolve this potential ambiguity, we delve deeper into the language of § 201.51(g). Importantly, for our purposes, the phrase "liquid drug in ampules or vials" is modified by the phrase "intended for injection." In contrast, the phrase "solid drug in ampules or vials" includes no such modifier. We conclude that this textual difference resolves the potential dilemma before us for two reasons. First, we conclude that the

phrase "intended for injection" makes clear, and reasonably so, that it is the form of the drug when administered to a patient that controls. Second, and relatedly, it is undisputed that Herceptin is "intended for injection" into patients. Indeed, the plaintiffs' claims in this case arise from the fact that they have been unable, after reconstituting vials of Herceptin, to withdraw the labeled amount of the drug for injection into patients. We therefore conclude that Herceptin constitutes a "liquid drug" for purposes of § 201.51(g). As such, its labeling has to "express the minimum quantity" of drug contained in each vial. 21 C.F.R. § 201.51(g).

Because the regulatory language resolves the question before us, we need not, and indeed cannot, under *Kisor*, defer to the FDA's interpretation of § 201.51(g) as applied to Herceptin. 139 S. Ct. at 2415. That said, we note, for what it is worth, that the FDA has likewise concluded that Herceptin constitutes a "liquid drug" for purposes of § 201.51(g), and Genentech "offer[s] no argument that the FDA's interpretation is plainly erroneous." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 615 (2011).[10] Although Genentech asserts, and the district court concluded, that the FDA treated Herceptin as a "solid drug" prior to 2014, we find no credible evidence in the record to support that assertion. And, even if such evidence existed, it would be entitled to no deference under *Kisor*.

[10] *Mensing* addressed only impossibility pre-emption. But we believe our reliance on it for the narrow point outlined above is accurate.

Having sorted through the federal statutory and regulatory framework that applies to Herceptin, we have little trouble concluding that the state law claims asserted by plaintiffs in this case are consistent with, and thus do not pose an obstacle to, the federal framework. Plaintiffs assert, in pertinent part, that a state can permissibly hold Genentech responsible for ensuring that every vial of Herceptin distributed to healthcare providers contains at least 440 mg of trastuzumab.[11] Such a state standard would be consistent with the requirements of § 201.51(g). As we have noted, § 201.51(g) requires that the product labels for liquid drugs in vials that are intended for injection, such as Herceptin, must "express the minimum quantity" of drug contained in each vial. 21 C.F.R. § 201.51(g). Because the product labels of the vials of Herceptin that were sold to plaintiffs all stated that the vials contained 440 mg of trastuzumab, § 201.51(g) effectively required those vials to all contain at least 440 mg of trastuzumab. Therefore, the federal regulatory standard is precisely the same as the state law standards sought to

[11] The various complaints that plaintiffs filed did not identify precisely what state standards they were seeking to impose on Genentech. In their subsequent pleadings, however, plaintiffs have made clear that they are asserting that the various state laws relied on in their respective complaints required Genentech to ensure that *every* vial of Herceptin distributed "contain[ed] ***at least***" "440 mg of trastuzumab," but that "reasonable variations between 440 and 475 mg" of trastuzumab were permissible. Aplt. Br. at 27 n.5, 32 (emphasis in original); *see also id.* at 48 (asserting that 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.").

be imposed by plaintiffs.[12] Consequently, the doctrine of obstacle pre-emption does not bar plaintiffs' claims.

Impossibility pre-emption

Impossibility pre-emption exists "when it is impossible for a private party to comply with both state and federal requirements." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019) (quotations omitted). "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Mensing*, 564 U.S. at 620. Therefore, impossibility pre-emption exists where fulfilling the state-law duties alleged by the plaintiff would require the defendant to "violate[] federal law." *Id.* at 618. "Impossibility pre-emption is a demanding defense." *Wyeth*, 555 U.S. at 573. The burden of establishing impossibility rests on the defendant. *Id.*

Genentech argued in its motion for summary judgment that it would be impossible for it "to comply with both federal law and the purported state-law dut[ies]" alleged by plaintiffs. Aplt. App., Vol. 7 at 1385 (capitalization omitted). Genentech argued in support, in pertinent part:

> To ensure each [multi-dose] vial [of Herceptin] contains no less than 440 mg, Genentech would have to modify its manufacturing processes and

[12] Genentech, in addressing the issue of obstacle pre-emption in its summary judgment motion, did not specifically discuss if or how that doctrine applied to plaintiffs' drug substance concentration and fill weight claims. Aplt. App., Vol. 7 at 1379-85. We therefore conclude that Genentech failed to establish that obstacle pre-emption applied to those claims.

> change the protein-content specification from 405-475 mg, to a new range with a minimum of at least 440 mg and a new upper limit. (Swisher Decl. ¶ 15.) The new target weight would have to be "well above" 440 mg. (*Id.*) Federal law requires prior FDA approval to make this change. (Lin Decl. ¶¶ 72-74.) 21 C.F.R. § 601.12(f)(1).
>
> * * *
>
> To the extent Plaintiffs are alleging Genentech had a state-law duty to provide Herceptin in vials that resulted in a concentration of exactly 21 mg/mL, or a volume of 20.952 mL, after reconstitution, those claims fail for the same reasons. Even if Genentech *could* ensure this precise concentration or volume (and the whole point of the reasonable-variation requirement is that manufacturers cannot ensure that kind of precision), it could not do so without changing its manufacturing processes and specifications. Because that requires prior FDA approval, Plaintiffs' attempt to require such changes by means of a state-law action is preempted.
>
> * * *
>
> Likewise, to the extent Plaintiffs are contending that Genentech is subject to a state-law duty to provide different labeling for Herceptin, any such claims are preempted because Genentech cannot do that without FDA's prior approval . . . .

Id. at 1388-89.

We reject Genentech's arguments for several reasons. To begin with, we note that Genentech's impossibility pre-emption arguments, like their obstacle pre-emption arguments, rest on the assumption that Herceptin is a "solid drug" for purposes of 21 C.F.R. § 201.51(g), and that, as a result, the product label for Herceptin merely had to "express the accurate net weight" of the product. More specifically, Genentech's impossibility pre-emption arguments rest on the assumption that it was permissible under § 201.51(g) for the contents of vials of Herceptin to vary within a range both below and

above the labeled amount, and that, in turn, the duty imposed on Genentech by federal law differs from the duty sought to be imposed on it by plaintiffs' state law claims. As we have discussed, however, Herceptin is a "liquid drug" for purposes of 21 C.F.R. § 201.51(g), and, consequently, federal law requires that Herceptin's labeling "express the minimum quantity" of drug contained in each vial. 21 C.F.R. § 201.51(g). Therefore, contrary to the assumptions made by Genentech in its summary judgment motion, the duty imposed on Genentech by § 201.51(g) is the same as the duty sought to be imposed by plaintiffs' state law claims: to ensure that the amount of trastuzumab contained in each vial is equal to or greater than the amount listed on the label.

That still, of course, leaves the question of whether Genentech has established that it would be impossible under the federal regulatory scheme for it to independently fulfill this duty, i.e., without first obtaining FDA preapproval for any necessary manufacturing or labeling changes. Under the FDA's regulatory scheme for biologics, "an applicant must inform the" FDA "about each change in the product, production process, . . . or labeling established in the approved license application(s)." 21 C.F.R. § 601.12(a)(1). "Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." *Id.* § 601.12(a)(2).

Changes other than those involving labeling fall into three general categories. "A supplement" to the BLA "shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." *Id.* § 601.12(b)(1). Such changes are deemed to be "major" for purposes of the regulatory scheme. *Id.* § 601.12(b). Changes that have a "moderate potential" for an "adverse effect" may be made by giving the FDA notice of the changes through a "Changes Being Effected in 30 Days" (CBE) notice. *Id.* § 601.12(c)(1). Lastly, changes are considered "minor" if they have a "minimal potential" to have an "adverse effect," and may be made immediately and described in the manufacturer's annual report. *Id.* § 601.12(d). The parties essentially agree, as do we, that, of these three categories, only "major" changes under § 601.12(b) generally give rise to impossibility pre-emption.[13]

Labeling changes likewise fall into three general categories: (1) labeling changes that require the submission of a supplement and FDA approval before the product can be distributed with the labeling change; (2) labeling changes that require the submission of a supplement but that can be implemented on distributed products prior to FDA approval;

[13] Because changes that have a "moderate potential" for an "adverse effect" can be made without FDA preapproval, they typically do not give rise to impossibility pre-emption. The only narrow exception occurs in those circumstances where a manufacturer can prove by "clear evidence that the FDA would not have approved a change." *Wyeth*, 555 U.S. at 571; *Mensing*, 564 U.S. at 624 n.8.

and (3) labeling changes that simply require submission in an annual report.[14] *Id.* § 601.12(f)(1)-(3).

As noted, Genentech argued in its motion for summary judgment, in pertinent part, that, to comply with the state law duty alleged by plaintiffs, it "would have to modify its manufacturing processes and change the protein-content specification from 405-475 mg, to a new range with a minimum of at least 440 mg and a new upper limit," and with a "new target weight . . . well above 440 mg." Aplt. App., Vol. 7 at 1388 (quotations omitted). Genentech in turn argued that this would "require[] prior FDA approval." *Id.* (citing 21 C.F.R. § 601.12(f)(1)). To support these arguments, Genentech cited to declarations from David Lin, a consulting scientist, and Dana Swisher, a Genentech employee and the Drug Product Technical Leader for Herceptin. Notably, Lin's declaration on this particular topic relied, in large part, on information provided to him by Swisher. According to Lin and Swisher, "[d]ue to filling equipment limitations, increasing the lower fill limit to 440 mg would increase the upper fill limit beyond the

[14] As we have noted, in August 1999, the FDA directed Genentech to revise the original labeling for Herceptin to omit the statement that each vial, after reconstitution, would yield a "21 mL" solution. Genentech could have at that point also proposed additional changes to the product label to make clear to healthcare providers that each multi-dose vial of Herceptin was unlikely to yield the "440 mg" of trastuzumab listed on the label. For example, as the FDA ultimately directed Genentech to do in 2017, Genentech could have proposed revising the product label from 440 mg per vial to 420 mg per vial. Or, alternatively, Genentech could have proposed revising the label to be consistent with the original BLA, which stated that Herceptin drug vials were "filled to deliver 400 mg trastuzumab." Given the FDA's actions in August 1999 and in early 2017, the FDA would almost certainly have approved either of those proposed revisions.

current FDA-approved limit of 475 mg, and would mean the new target fill weight would have been considerably higher than 440 mg." *Id.* at 1479 (Lin Declaration ¶ 73); *see id.* at 1507-08 (Swisher Declaration ¶15).

We conclude, however, that the evidence in the record regarding impossibility is neither undisputed nor as one-sided as Genentech would have us believe. Focusing first on the opinions offered by Swisher, we agree with plaintiffs that "Swisher acknowledged he made no attempt to determine," or in turn explain, "why the vast majority of Herceptin batches measured after 2009 contained less than the labeled amount of trastuzumab." Aplt. Br. at 44 (emphasis omitted). We further agree with plaintiffs that there is no evidence that Swisher "conduct[ed] 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." *Id.* We therefore decline to accept at face value Swisher's assertion that it would be impossible for Genentech to satisfy the duty alleged by plaintiffs without making major changes to its manufacturing processes.

Moreover, we conclude that the evidence submitted by plaintiffs in opposition to Genentech's motion for summary judgment undercuts Swisher's declaration and, in turn, Genentech's assertion of impossibility. Plaintiffs, in their response to Genentech's motion for summary judgment, submitted evidence indicating that, for every year between 1998 and 2007 (with the exception of 1999), the mean trastuzumab content per vial of Herceptin produced by Genentech exceeded 440 mg. Aplt. App., Vol. 8 at 1651.

More specifically, the mean trastuzumab content per vial during that time ranged from 440.70 mg (in 2003) to 455.73 mg (in 1998). *Id.* The evidence submitted by plaintiffs further established that, from 2008 through 2017, the mean trastuzumab content per vial of Herceptin consistently fell below 440 mg. *Id.* This ranged from a mean low of 428.64 mg per vial in 2012 to a mean high of 439.94 mg in 2008. *Id.* In the last six years of that ten-year time period, the mean content typically hovered near 430 mg per vial. *Id.* Further, only one of the 125 batches measured in the three-year period between 2012 and 2014 contained at least 440 mg of trastuzumab per vial. *Id.* at 1652. Notably, Genentech does not dispute this evidence, nor does it offer any explanation for the downward trend.

Relatedly, plaintiffs submitted evidence that, during the period from 2009 to 2013, Genentech's lower control limit for Herceptin multi-dose vials manufactured at one of its manufacturing facilities was 427 mg of trastuzumab per vial, and its upper control limit was 446 mg trastuzumab per vial. *Id.* at 1661. This represents a range of only 19 mg and the center of that range is 436.5, not the 440 mg target established by the FDA. *Id.* Plaintiffs also submitted evidence indicating that, between 2010 and 2016, more than 99% of Herceptin batches that were distributed by Genentech fell within a range of 414.9 mg to 451.5 mg of trastuzumab per vial. *Id.* This is a variance of 36.6 mg (± 18.3 mg), far lower than the 70 mg variance listed in the BLA. *Id.*

This evidence, we conclude, suggests that Genentech, as it continued to manufacture Herceptin, obtained and exercised a high degree of control over its manufacturing process, and, in turn, may have knowingly targeted an amount of

trastuzumab per vial lower than the 440 mg target stated in the BLA. In other words, the evidence suggests that the downward trend of the average quantity of trastuzumab per vial was not the result of "unavoidable deviations in good manufacturing practice," but instead may have been the result of intentional acts on the part of Genentech. 21 C.F.R. § 201.51(g). As plaintiffs' expert statistician, Dr. William Huber, opined, "[i]f Genentech targeted 440 mg of trastuzumab per vial, reasonable variation would consist of approximately half of the vials containing more than 440 mg and approximately half of the vials containing less than 440 mg." Aplt. App., Vol. 8 at 1653. Thus, "[t]he [actual] variations in Herceptin drug product protein content" do not appear to us to have been "random variations around 440 mg/vial." *Id.*

We therefore agree with plaintiffs, as they argued in response to Genentech's motion for summary judgment, that there is "no evidence that any of the fluctuations in Herceptin's protein content through the years resulted from changes to the upper (or lower) limits of its specification," and that "[t]his historical data is, in itself, sufficient to rebut Genentech's claim that it cannot consistently produce vials containing at least 440 mg trastuzumab within its current specifications." *Id.* at 1711.

One other related point deserves mentioning because it supports our conclusion that Genentech failed to establish impossibility. Plaintiffs, in their response to Genentech's motion for summary judgment, argued that Genentech could have satisfied its state law duty of ensuring that every multi-dose vial of Herceptin contained at least 440 mg of trastuzumab by simply targeting a higher drug substance concentration within

the FDA-approved concentration range. Although Genentech disputes this point, the evidence in the record tends to support plaintiffs' argument and undercut Genentech's arguments to the contrary.

According to the record, the amount of trastuzumab per vial is the product of the drug substance concentration, which has an FDA-approved range of 24 to 26 mg/mL, and the vial fill weight, which has an FDA-approved range of 17.56 to 18.28 grams.[15] During the entire time period that Genentech produced multi-dose vials of Herceptin, the drug substance concentration numbers varied from 23.5 to 26.4 mg/mL per batch. That said, the average drug substance concentration per batch was largely above the target of 25 mg/mL from 1998 until 2009.[16] In 2010, however, the average drug substance concentration per batch fell to 24.65 mg/mL. And the average drug substance concentration per batch remained below 25 mg/mL until 2015, when it rose to 25.05 mg/mL. *Id.* All of which strongly suggests that Genentech intentionally targeted these lower drug substance concentrations over time (without simultaneously increasing its target fill weights) and, as a result, intentionally, or at least knowingly, allowed the

[15] More specifically, the vial fill weight is divided by the density of Herceptin (1.01 g/mL) to account for the lyophilization of the liquid drug substance. Aplt. App., Vol. 14 at 3356. This results in a "fill volume," which is then multiplied by the drug substance concentration to produce the total amount of trastuzumab for the vial. *Id.*

[16] In 2003, Genentech changed the drug substance from version 1.0 to version 1.1. The change to version 1.1 led to significantly lower variation in the drug substance concentration per batch. Specifically, Genentech's internal records indicate that Genentech was "reliably capable of producing to within ±0.25 mg/mL" of its target drug substance concentration per batch. Aplt. App., Vol. 10 at 2412.

average amount of trastuzumab per vial to drop below 440 mg per vial for an extended period of time.

The evidence suggests that if Genentech maintained the same target fill weight ranges that it previously employed at its manufacturing facilities (those ranges varied slightly from one facility to another) and targeted a drug substance concentration per batch between 25.5 and 26.0 mg/mL (within the FDA-approved specification range), this would have ensured that the trastuzumab content exceeded 440 mg per vial. For example, employing the fill weight control limit low of 17.56 grams per vial and a drug substance concentration per batch of 25.5 mg/mL would have resulted in a trastuzumab content per vial of 443.3 mg. Even employing the fill weight control limit high of 18.28 grams per vial and a drug substance concentration per batch of 26 mg/mL would have resulted in a trastuzumab content per vial of 470.6 mg, an amount that still fell within the upper limit of the FDA-approved range.

To be sure, Genentech argues that increasing the drug substance concentration per batch would have required it to change the diluent specification, and that in turn would have required FDA approval. But, as we have noted, the historical data indicates that, from 2009 forward, Genentech consistently produced batches of Herceptin with drug substance concentrations that fell below the FDA-approved 25 mg/mL target, and without seeking or obtaining FDA approval for a change in the diluent specification. Notably, Genentech fails to explain this apparent inconsistency, i.e., why drug substance concentrations that fall within the lower end of the FDA-approved range (but below the

FDA-approved target) do not require a change in the diluent specification, but drug substance concentrations that fall within the upper end of the FDA-approved range do require such a change.

For all of these reasons, we conclude that Genentech has failed to conclusively establish either that employing a target range of 440 mg to 475 mg of trastuzumab per vial, or targeting a drug substance concentration per batch between 25 and 26 mg/mL, would have resulted in a "major" change under 21 C.F.R. § 601.12(b) that required FDA preapproval. In other words, we conclude, for the reasons outlined above, that Genentech has failed to establish that it could not have independently implemented these changes in order to comply with the state law duties alleged by plaintiffs.[17]

That leaves one final subject to address in terms of impossibility pre-emption. As we have noted, plaintiffs separately alleged that Genentech falsely represented and warranted on its product labels that "[e]ach reconstituted vial of Herceptin yield[ed] fluid solution with a density [or concentration] of 21 mg/mL." Aplt. App., Vol. 2 at 417. Genentech's motion for summary judgment briefly addressed this claim, but gave short shrift to it. Genentech argued, in summary fashion, that it could not "ensure th[e] precise

[17] Genentech's motion for summary judgment summarily addressed the applicability of impossibility pre-emption to plaintiffs' solution claim. Aplt. App., Vol. 7 at 1388-89. Specifically, Genentech argued that impossibility pre-emption applied to the solution claim "for the same reasons" as plaintiffs' trastuzumab content claim. *Id.* at 1388. Having rejected Genentech's impossibility pre-emption arguments as to the trastuzumab content claim, we likewise conclude that Genentech has failed to establish the applicability of impossibility pre-emption to plaintiffs' solution claim.

concentration . . . without changing its manufacturing processes or specifications." *Id.*, Vol. 7 at 1388-89. Genentech also argued, in two brief paragraphs, that it could not change the product labeling without prior FDA approval. *Id.* at 1389-90. Plaintiffs, in their response to Genentech's summary judgment motion, stated it was not their contention that "Genentech should have changed its manufacturing process to ensure the concentration matched the statement on the Herceptin labeling," but rather that "Genentech should have accurately stated the drug concentration on the labeling." *Id.*, Vol. 8 at 1715. Plaintiffs argued that Genentech could have independently changed its product labeling to more accurately reflect the product concentration, without FDA preapproval, by utilizing the "Changes Being Affected" (CBE) process outlined in 21 C.F.R. § 601.12(f)(2)(i)(C). The district court granted summary judgment in favor of Genentech on this claim, but in doing so stated simply, without explanation, that "[c]hanging the concentration stated on the label . . . . would require FDA approval. 21 C.F.R. § 601.12(f)(1)." *Id.*, Vol. 6 at 1336.

After reviewing the record on appeal, we conclude that Genentech's arguments on this issue were inadequately developed, and that, in any event, the evidence submitted by Genentech in support of its arguments was insufficient to allow us to arrive at any reasonable conclusion regarding the impossibility of Genentech utilizing the CBE process to change the drug concentration statements on its product labeling. Genentech therefore failed to establish its entitlement to summary judgment as to this claim, and the district court erred in concluding otherwise.

In summary, we conclude, for the reasons outlined above, that Genentech has failed to satisfy its burden of establishing that impossibility pre-emption applies to plaintiffs' claims.

III

The district court's grant of summary judgment in favor of Genentech is REVERSED and the case REMANDED to the district court for further proceedings. Plaintiffs' motions to seal their opening brief, reply brief, and appendix are GRANTED.