No. 19-5035

IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

In re: Genentech, Inc. Herceptin (Trastuzumab) Marketing and Sales Practices Litigation (MDL 2700)

TULSA CANCER INSTITUTE, PLLC, *et. al.*,

Plaintiffs/Appellants,

v.

GENENTECH, INC.,

Defendant/Appellee.

On Appeal from United States District Court, Northern District of Oklahoma,
Case Nos. 4:16-MD-02700-TCK-JFJ, 4:15-CV-00157-TCK-JFJ, 4:16-CV-00202-TCK-JFJ, 4:16-CV-00203-TCK-JFJ, 4:16-CV-00204-TCK-JFJ, 4:16-CV-00206-TCK-JFJ, 4:16-CV-00205-TCK-JFJ, 4:16-CV-00207-TCK-JFJ, 4:16-CV-00210-TCK-JFJ, 4:16-CV-00221-TCK-JFJ, 4:16-CV-00347-TCK-JFJ, 4:16-CV-00359-TCK-JFJ, 4:16-CV-00419-TCK-JFJ, 4:16-CV-00424-TCK-JFJ, 4:17-CV-00394-TCK-JFJ

The Honorable Terence C. Kern, United States District Judge

BRIEF OF *AMICI CURIAE* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, NATIONAL ASSOCIATION OF MANUFACTURERS, AND BIOTECHNOLOGY INNOVATION ORGANIZATION IN SUPPORT OF AFFIRMANCE

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CORPORATE DISCLOSURE STATEMENT

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Dated: October 11, 2019

/s/ K. Lee Marshall
K. Lee Marshall

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INTEREST OF AMICI CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies. PhRMA's mission is to advocate for public policies that encourage the discovery of life-saving and life-enhancing medicines that help patients lead longer, healthier, and more productive lives. New therapies from PhRMA members have contributed to a 27% decrease in cancer deaths and have increased the life expectancy of cancer patients by 41%. PhRMA, *Biopharmaceuticals in Perspective, Summer 2019*, at 6 (2019), *available at* https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA Org/PDF/PhRMA_2019_ChartPack_Final.pdf (hereafter "*Biopharmaceuticals in Perspective*"). PhRMA members invested nearly $80 billion in 2018 researching and developing new medicines. *Biopharmaceuticals in Perspective* at 40.

The National Association of Manufacturers ("NAM") is the nation's largest manufacturing association, representing small and large manufacturers in every industrial sector and in all 50 states. Manufacturing employs over 12 million men and women, contributes $2.25 trillion to the U.S. economy annually, and accounts for more than three-quarters of all private-sector research and development. The NAM is the voice of the manufacturing community and the leading advocate for a policy agenda that helps manufacturers compete in the global economy and create jobs across the United States.

The Biotechnology Innovation Organization ("BIO") is the largest biotechnology organization in the world, providing advocacy, business development, and communications services for more than 1,250 members worldwide. BIO members are involved in researching and developing innovative healthcare, agricultural, industrial, and environmental biotechnology products. Corporate members range from entrepreneurial companies developing a first product to Fortune 100 multinationals. BIO also represents state and regional biotech associations, academic centers, venture capital firms, and other service providers to the industry.

This case is of critical importance to *amici* members because it threatens manufacturers' ability to rely on specifications approved by the Food and Drug Administration ("FDA") when developing and manufacturing new medicines. Permitting states to second-guess the appropriateness of FDA-approved drug specifications would inject unnecessary post-approval costs and uncertainty that could impede access to medicine.[1]

[1] All parties have consented to the filing of this brief. *See* Fed. R. App. P. 29(a)(2). No party's counsel authored this brief in whole or in part; no party or party's counsel contributed money that was intended to fund the preparation or submission of this brief; and no person other than amici, their members, and their counsel contributed money that was intended to fund the preparation or submission of this brief. *See* Fed. R. App. P. 29(a)(4)(e).

SUMMARY OF ARGUMENT

FDA utilizes its expertise to approve drug specifications and labeling both before and after a medicine is approved for sale. *See* 21 C.F.R. §§ 314.50, 314.70(b), 601.2(a), 601.12(b). Most relevant to this case, FDA approves a net weight specification (*i.e.*, quantity) that allows for "reasonable variations" in the amount of medicine contained in each packaged form to account for inherent variability in manufacturing. 21 U.S.C. § 352(b); 21 C.F.R. § 201.51(g); Brief of Defendant-Appellee at 4.

Reversal of the district court's grant of summary judgment on preemption grounds would threaten pharmaceutical manufacturers' ability to rely on FDA-approved specifications. There is no evidence that any vial of Herceptin failed to contain between 405 mg and 475 mg of trastuzumab, which is the net weight range FDA deemed appropriate to deliver the intended amount of 400 mg of trastuzumab. Yet, Plaintiffs claim under various state laws Herceptin vials should contain at least 440 mg of trastuzumab, because they disagree with the accuracy of FDA's approved labeling that states each vial "nominally" contains 440 mg.

Permitting states to impose net weight specifications that diverge from FDA-approved specifications would stand as an obstacle to FDA's implementation of federal objectives. The cost to innovate and obtain FDA approval for new medicines is substantial. Injecting risk that states may second-guess the specifications FDA approved could increase the costs and uncertainty associated

with the already expensive and unpredictable drug development process. That is self-evident here, where Plaintiffs concede their claims would "mandate[]" Genentech either "discard" all FDA-approved vials of Herceptin that contain between 405 mg and 439 mg of medicine or incur significant costs to redesign its manufacturing processes to comport with Plaintiffs' divergent net weight specification. Opening Brief of Plaintiff-Appellants at 50-51.

The court should affirm the district court's judgment below.

ARGUMENT

I. FDA Utilizes its Expert Judgment to Specifically Approve and Regulate the Net Weight Ranges for All Medications.

A. Biologics are Complex Medicines Created from Cutting Edge Bio-Technology.

Herceptin is a prescription biologic that prevents the spread of cancer in patients with HER2-positive breast cancer, an aggressive form of cancer that represents approximately 20% of breast cancers. Ajoy Dias, et. al., *Human epidermal growth factor antagonists and cardiotoxicity-A short review of the problem and preventive measures*, 104 Critical Reviews in Oncology/Hematology 42, 43 (2016). Biologics like Herceptin are developed from human, animal, or microorganism sources, using cutting-edge biotechnologies, to treat medical conditions for which no other treatments are available. *What Are "Biologics" Questions and Answers*, U.S. Food and Drug Administration, https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-

cber/what-are-biologics-questions-and-answers (last accessed 9/30/2019); *see also* 42 U.S.C. § 262(i)(1) ("The term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.").

Biologics are different from conventional drugs in several respects. Conventional drugs are created in a laboratory through chemical synthesis and are typically small in molecular structure. *See* Congressional Research Service, *Biologics and Biosimilars: Background and Key Issues*, at 1-2 (June 6, 2019), *available at* https://fas.org/sgp/crs/misc/R44620.pdf (last accessed 9/30/2019). Biologics by contrast are created in host cells from living organisms and possess more complex molecular structures. *Id.*; *see also* Leigh Revers & Eva Furczon, *An Introduction to Biologics and Biosimilars. Part II: Subsequent Entry Biologics: Biosame or Biodifferent?*, 143 No. 4 Canadian Pharmacists Journal 184, 184-185 (July 1, 2010) (describing biologics as "behemoths when comparing their relative molecular mass . . . to even the largest of conventional drugs.").[2] Biologics "are far too large and structurally demanding to be prepared effectively by organic

[2] The reason for the increased size of biologics is their molecular structures: most biologics are "biopolymers of typically several hundred amino acids . . . , biochemically strung together in a defined sequence by peptide bonds to form a polypeptide." Revers & Furczon, *An Introduction to Biologics and Biosimilars. Part II*, 143 No. 4 Canadian Pharmacists Journal at 184.

synthesis." Revers & Furczon, *An Introduction to Biologics and Biosimilars. Part II*, 143 No. 4 Canadian Pharmacists Journal at 185.[3] Rather, they must be manufactured through a complex, multi-stage, biological process that introduces variability at each stage.

The manufacturing process for most biologics comprises several phases: (1) host-cell selection and development, (2) master cell bank establishment, (3) protein production, (4) purification, (5) analysis, (6) formulation, and (7) storage and handling. *Id.* at 187. Each of these phases is independently variable, complex, and capable of altering the final biologic. Arnold G. Vulto & Orlando A. Jaquez, *The Process Defines the Product: What Really Matters in Biosimilar Design and Production?*, Rheumatology, iv14, iv18 (2017); W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 Iowa L. Rev. 1023, 1035 (2016) ("[F]inal therapeutic proteins are influenced by each step in the manufacturing process.").[4]

The first manufacturing phase, host-cell selection and development, is essentially an unpredictable process:

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[3] *See also* Leigh Revers & Eva Furczon, *An Introduction to Biologics and Biosimilars. Part I: Biologics: What Are They and Where Do They Come From?*, 143 No. 3 Canadian Pharmacists Journal at 134 (May 1, 2010) ("Compared to the more traditional drugs, such as Aspirin, this new class of medicine is inherently more complex and cannot be synthesized in the laboratory by chemical means alone.")

[4] "Even slight alterations in any of these stages can lead to significant changes in protein structure . . . , with clinical implications for safety, immunogenicity and potency." Revers & Furczon, *An Introduction to Biologics and Biosimilars. Part II*, 143 No. 4 Canadian Pharmacists Journal at 187.

> A starter population of cells is selected from among several possibilities (bacterial, yeast or cells from mice or hamsters) and DNA encoding the protein of interest is added to the cells. This DNA is taken up in essentially random amounts. To leverage this random distribution of both the number and location of gene copies, the cells are isolated, grown into populations, and evaluated for growth and production rates.

Price & Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 Iowa L. Rev. at 1034 (internal footnotes omitted). The subsequent manufacturing phases also have inherent variability "as they turn on the interaction of the cell line with a complex environment." *Id.* at 1033, 1035 ("[T]he specific contours of manufacturing processes, including the selection of the host organism, the identification of a particular cell line, culture and media conditions, and purification procedures, all impact the characteristics and activity of the final product.").[5]

Even after most biologics are produced and purified, variability continues throughout the filling process. Biologics require strict filling, storage, and handling requirements because they are typically "extremely sensitive to physical conditions." Thomas Morrow, *Defining the Difference: What Makes Biologics Unique*, Biotechnology Healthcare 24, 26 (September 2004). Unlike most conventional medicines, which can be mass produced in tablet, capsule, or

[5] "In addition to normal batch-to-batch variability and drift, additional changes in product quality may be the result of intentional changes made by the manufacturers of biological medicines to the manufacturing process and can range from changes in manufacturing sites to changes in suppliers or cell culture media." Vulto & Jaquez, *The Process Defines the Product*, Rheumatology, at iv18.

injectable form, some biologics like Herceptin "are required to be shipped chilled in the form of freeze-dried powders that must be reconstituted with vehicle and the resulting drug solution must either be used immediately or stored in the refrigerator and soon discarded." Revers & Furczon, *An Introduction to Biologics and Biosimilars. Part II*. 143 No. 4 Canadian Pharmacists Journal at 185 ("Since proteins are large and inherently unstable in the presence of proteases and since solutions of proteins can also support the growth of contaminating bacteria, the complex structural integrity of biologics is easily compromised."). A filling machine is often used to dispense the biological product into vials that are then loaded into a lyophilizer to be freeze-dried. AA 7/1506. Factors such as temperature, friction, shear forces, chemical phase, and piping mechanics all lead to variation in fill weight. Morrow, *Defining the Difference*, Biotechnology Healthcare at 26. These complex filling, storage, and handling requirements further contribute to the final biologic's variability.

In light of these manufacturing complexities, variability in the manufacturing of biologic medicine is the rule, not the exception. Vulto & Jaquez, *The Process Defines the Product,* Rheumatology, at iv18 ("As each step of the manufacturing process has multiple process parameters that can alter the quality of the product, the manufacturing process for biologics is highly challenging . . . ."); Revers & Furczon, *An Introduction to Biologics and Biosimilars. Part II*, 143 No. 4 Canadian Pharmacists Journal, at 187 ("It comes as no surprise, then, that the

manufacture of [biologics] is fraught with technical difficulties associated with reproducibility and with the careful and precise control of all conceivable parameters during production."). The Congressional Research Service, in a recent report prepared for members and committees of Congress, recognized this very point, noting that "[b]ecause biologics are . . . complex . . . both in composition and method of manufacture," there is "inherent variability in biological products from natural sources." Congressional Research Service, *Biologics and Biosimilars*, at 8.

B. Net Weight Specifications Should Be Determined by an Expert Regulator and Not Patchwork Litigation of State Law Claims.

Congress recently observed that "for many years . . . the drug industry and FDA have coped with the inherent variability in biological products." Congressional Research Service, *Biologics and Biosimilars*, at 8. Specifically, FDA has developed and implemented "control strategies" to ensure that biologics are clinically safe and effective notwithstanding their inherent variability, explaining that:

> The nature of biological products, including the inherent variations that can result from the manufacturing process, can present challenges in characterizing and manufacturing these products that often do not exist in the development of small molecule drugs. Slight differences between manufactured lots of the same biological product (i.e., acceptable within-product variations) are normal and expected within the manufacturing process. As part of its review, FDA assesses the manufacturing process and the manufacturer's strategy to control within-product variations. These control strategies are put in place to

> help ensure that manufacturers produce biological products with consistent clinical performance.

Biological Product Definitions, U.S. Food and Drug Administration, https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf (last accessed 9/30/2019).

Biologics are at the forefront of medicine and federal policy. Congressional Research Service, *Biologics and Biosimilars* at 8. FDA has years of experience and expertise managing the inherent variability of biologics and is therefore best positioned to determine the specifications that ensure biologics are clinically safe and effective. State law claims that second-guess FDA's expert judgment thwart Congress's intended regulatory scheme.

C. Federal Law Permits "Reasonable Variations" in Net Weight.

One area that biologics may vary during manufacture is net weight. *See* Brief of Defendant-Appellee at 4. Congress and FDA recognize that some variability in the quantity of medicine in each packaged form is inevitable due to the complicated processes required to fill biological products into useable delivery systems. The Federal Food Drug and Cosmetic Act ("FDCA") therefore makes it lawful for prescription medicines to contain "reasonable variations" from the "quantity" of medicine listed on the label. 21 U.S.C. § 352(b). Congress directed FDA to determine acceptable variations for medicines. *Id*. The FDCA's safe-harbor permitting the quantity of medicine in each package to vary is consistent

with FDA's "longstanding administrative practice" to "permit[] reasonable variations from stated net weight" for food and drugs. *Jones v. Rath Packing Co.*, 430 U.S. 519, 537 (1977).

Pursuant to its congressional directive, FDA promulgated regulations identifying the amount medicines may vary from the quantity stated on their labels. 21 C.F.R. § 201.51(g). Through its expert judgment, FDA permits a "solid drug in ampules or vials" like Herceptin to have a net weight variability that "compl[ies] with the limitations provided in the U.S. Pharmacopeia" ("USP").[6] *Id.* The USP permits Herceptin vials, for example, to vary up to 15% from its quantity stated on its labeling. *See* AA 7/1460–61.

D. FDA's Approved Net Weight Specification for HerceptinPermits a 35 mg Variance from the 440 mg Labeling Claim.

A manufacturer must submit a Biologic License Application ("BLA") to FDA before selling the biologic. *See* 42 U.S.C. § 262(a). The BLA is the company's "request for permission" to sell the biologic and it must contain detailed manufacturing information, preclinical studies, clinical studies, and labeling for FDA's approval. *Biologics License Applications (BLA) Process (CBER)*, U.S. Food and Drug Administration, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-

[6] The USP is a pharmacopeia published annually by the United States Pharmacopeial Convention, which is a nearly 200 year old nonprofit that develops scientific drug standards that help ensure the quality and safety of medicines in the United States. *Advancing quality: our progress*, USP, https://www.usp.org/about/annual-report (last accessed Sept. 30, 2019).

applications-bla-process-cber (last accessed October 1, 2019); *see also* 21 C.F.R. §§ 601.2(a), 600.3(kk). FDA must evaluate the submitted information and determine the product is safe, pure, and potent, and that its manufacturing process would not "impair . . . continued safety, purity, and potency." 21 C.F.R. §§ 601.2(d), 601.20(a), (c). A net weight range is a specification FDA approves to license a biologic. Brief of Defendant-Appellee at 4, 40.

FDA approved the BLA for Herceptin to deliver 400 mg of trastuzumab per vial; a net weight range between 405 mg and 475 mg of trastuzumab per vial; and labeling stating each vial "nominally" contains 440 mg of trastuzumab (i.e. the median of the net weight range). *Id.* at 4. FDA exercised its expert judgment concerning biologic medicines to require less variation than the USP's applicable 15% variation tolerance for Herceptin. FDA determined these specifications permitted *both* "reasonable variations" in the quantity of medicine in each vial *and* ensured that all vials could deliver *at least* the intended amount of 400 mg in FDA's expert view. *See* 21 U.S.C. § 352(b); 21 C.F.R. § 201.51(g).

FDA further approved the manufacturing processes described in Herceptin's BLA that were designed to produce the approved 405 mg to 475 mg amount. Food and Drug Administration Memorandum from J. Lloyd Johnson on Review of Genentech's rhuMAb HER2, BLA Ref. No. 98-0369, CMC section Volume 7, Facilities and establishment descriptions (Sept. 23, 1998), *available at* https://web.archive.org/web/20170114040232/http://www.fda.gov/downloads/

drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm091367.pdf (last accessed October 1, 2019). FDA determined that the Herceptin BLA "adequately address[ed] multi-product facility control issues and concerns with respect to product campaigning, product changeover, segregation procedures, cleaning validation, cross contamination precautions and testing" and that all "equipment, process controls, operating procedures, documentation and records" complied with FDA good manufacturing practices set forth in 21 C.F.R. Part 606. *Id.*

E. FDA Regulates Net Weight Post-Approval.

FDA maintains oversight of a biologic's net weight post-approval. FDA prohibits manufacturers from making any changes to the manufacturing process that would alter the approved net weight specification without FDA's permission. 21 C.F.R. § 601.12(b)(2)(i) (requiring FDA to approve changes "in the specifications provided in the approved application"); *Guidance for Industry, Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*, 1997 WL 33793763, at *3 (F.D.A. July 24, 1997) (stating that "[a]ny change in manufacturing processes" that "results in change(s) of specification limits" requires "the agency's continued premarket review and approval" for safety and efficacy reasons).

The Draft Guidance issued by FDA in 2014 concerning fill volumes for certain biologic products and the subsequent regulatory back-and-forth between

FDA and Genentech is consistent with this overall scheme of FDA expert regulatory primacy. It demonstrates FDA's post-approval oversight and its willingness to reevaluate its policies, including the interplay between net weight variability and label claims. AA 6/1086-1092, AA 7/1368. FDA's "current thinking" in 2014 that Herceptin's labeling should state the minimum amount of medicine in the vial was a change from its thinking sixteen years earlier when it approved a labeling claim of 440 mg that was the median of its approved net weight specification.

F. Plaintiffs' Claims Conflict with FDA's Expert Judgment.

Regardless of any evolution in FDA's implementation of net weight specifications and labeling, state law claims that second-guess FDA-approved specifications stand as an obstacle to the agency's exercise of its expert judgment. The Seventh Circuit recently reversed certification and dismissed state law claims that second-guessed the size of FDA-approved eye drops, reasoning that whether smaller drops "would be as or even more effective, and also cheaper" were "matters for the class . . . to take up with the FDA" because a federal court "cannot bypass the agency and make its own evaluation of the safety and efficacy" of FDA-approved medications. *Eike v. Allergan, Inc.*, 850 F.3d 315, 318 (7th Cir. 2017).

The net weight specification and labeling of Herceptin are similarly "matters for [Plaintiffs] to take up with FDA." FDA relied on its experience and expertise

managing the variability of biologics to approve Herceptin's net weight specification and labeling. There is no evidence that any vial of Herceptin failed to contain between 405 mg and 475 mg of trastuzumab as approved by FDA. Plaintiffs should not be able to interfere with FDA's judgment about net weight specifications and corresponding labeling under state law. This interference would pose an obstacle to FDA's implementation of the federal objective to permit reasonable variations in the quantity of medicine.

II. Permitting States to Impose Requirements that Conflict with FDA's Approved Specifications Could Harm Public Health by Increasing the Cost of Medicine and Reducing Access to Medicine.

A. Obtaining FDA Approval of a New Drug or Biologic is Time Consuming, Expensive, and Risky.

FDA oversees a multi-step development process for drugs and biologics: (1) Discovery and Development; (2) Preclinical Research (i.e. non-human testing); (3) Clinical Research (i.e. human testing); and (4) FDA Review. *The Drug Development Process*, U.S. Food and Drug Administration, *available at* https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process (last accessed October 2, 2019); *Biopharmaceutical Research & Development: The Process Behind New Medicines*, PhRMA (2015) at 3, 21-22, http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf (*Biopharmaceutical Research & Development")*. During the initial discovery and development phase, companies

research upwards of thousands of compounds to identify the ones that merit further study. *Id.* at 3-4. The preclinical phase involves laboratory and animal studies designed to assess the safety and efficacy of the compound before testing it in humans. *Id.* at 8; 21 C.F.R. § 312.23(a)(8). If the preclinical results are promising, the company submits an Investigational New Drug application ("IND") to FDA, proposing a plan for human clinical trials that FDA must review. 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)-(b). Clinical trials performed prior to approval typically occur in three phases. 21 C.F.R. § 312.21; *Biopharmaceutical Research & Development* at 13. On average, the clinical trial phase alone takes six to seven years to complete. *Biopharmaceutical Research & Development* at 13. When clinical trials show the benefits of the medicine outweigh the risks, the sponsoring company can request FDA's permission to market the medicine by submitting a New Drug Application ("NDA") or BLA. 21 U.S.C. § 355(b)(1); 21 C.F.R. § 601.2(a). These submissions contain the results of preclinical and clinical testing, manufacturing processes, and proposed labeling and often are more than 100,000 pages long. *Biopharmaceutical Research & Development* at 14.

Bringing a new drug or biologic to market is tremendously expensive. It costs a company on average $2.6 billion to develop and obtain FDA approval of a new prescription medicine. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 25-26 (2016); *Biopharmaceuticals in Perspective* at 33. Preclinical work costs

approximately $1.1 billion. *Id.* Clinical testing costs $1.5 billion, with Phase III trials costing $200 to $250 million in out-of-pocket expenditure alone. *Id.*

This significant investment in innovation is also fraught with risk: nearly all compounds fail to pass at least one of the development phases. *Biopharmaceutical Research & Development* at 1. Even of the few compounds that progress to clinical trials, only 12% of those ever obtain FDA approval. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry*, 47 J. Health Econ. at 23.

The cost and risk absorbed by companies to innovate cutting-edge medicines is at an all-time high. Since 2000, the cost of drug development has increased 166% in "real dollars," while the likelihood that a medicine ever obtains FDA approval has decreased by nearly 50%. *Id.* at 31; *Biopharmaceutical Research & Development* at 41.

B. State Mandated Changes to FDA-Approved Specifications Would Inject Substantial Post-Approval Development Costs that Could Stifle Innovation and Restrict Access to Life-Saving Medicine.

Access to innovative medicine could be impeded in three significant ways if each state is permitted to second-guess FDA-approved specifications and set their own: fewer new medicines could be brought to market; existing medicines could be removed from the market; and the price of medicines that were altered to comply with state requirements could increase. Paul A. Herbig & James E. Golden, *Innovation and Product Liability*, 23 Industrial Marketing Management 245, 246, 248-249 (1994); Richard Manning, *Economic Impact of Product*

Liability in US Prescription Drug Markets, 29 Int'l Bus. Law. 104, 108 (2001). Each potential outcome would deprive patients access to life-saving and life-enhancing medications they need.

Manufacturers evaluate litigation risk before incurring the substantial time, cost, and risk associated with developing and obtaining FDA's approval of new medicine. *See* Gideo Parchomovsky & Alex Stein, *Torts and Innovation*, 107 Mich. L. Rev. 285, 289 (2008) ("The greater the investment in R&D necessary to produce certain innovation, the greater is the risk that the innovation will not be produced."). Litigation risk has prompted manufacturers to "abandon new technologies, life-saving drugs, and innovative product designs." Herbig & Golden, *Innovation and Product Liability*, 23 Industrial Marketing Management at 249; s*ee also* W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418, 1419 (1994) ("[T]he net effect of the surge in liability costs ha[s] been to discourage innovation in the pharmaceutical industry."); Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L. Rev. 1139, 1153 (1987) ("If in the aggregate the net gains are wiped out by the liability costs, then the product will no longer be made."). Surveys indicate that as many as 1/4 or 1/3 of United States manufacturers have postponed or abandoned efforts to innovate and develop new products because of increasing liability risks. Herbig & Golden, *Innovation and Product Liability*, 23 Industrial Marketing Management at 249. Heightened

litigation risk creates "uncertainty" that "makes rational business planning impossible." *Id.* Indeed, "[w]here the liability problems have been most intense, manufacturers responded to the liability threat by not innovating." *Id.* at 245-246.

Litigation risk has also caused companies to pull safe and effective medicine from the market. For instance, in the 1980s, Merrell Dow stopped producing what was then the only antinausea drug prescribed for pregnant women because of the litigation costs (and the resulting increased insurance premiums). *Id.* at 250. This was true despite the fact that Merrell Dow had won nearly all of the lawsuits brought against it related to the antinausea drug. *Id.* "Even when a company wins lawsuits against it, the cost of coverage, litigation, and the fear of a possible large judgment against it can persuade management that a product is not worth selling." *Id.* at 249. Similarly, G.D. Searle and Company suspended production of the Copper-7 contraceptive intrauterine device after encountering nearly 800 lawsuits, most of which had been settled with only small payments. *Id.*; *see also* Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability*, 1976-1989, 24 Seton Hall. L. Rev. at 1418.

Finally, if states are able to require manufacturers to alter FDA-approved specifications, it would create uncertainty and add to the already significant costs to develop innovative medicines and delivery systems. In that case, companies would need to perform new "studies . . . to evaluate the effect of the change on the product's identity, strength, quality, purity, or potency" to justify the state

mandated changes to FDA. 21 C.F.R. § 601.12(b)(2)(i), (b)(3); *see also* Center for Drug Evaluation Research, *Guidance for Industry Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*, 1997 WL 33793763, at *2 (F.D.A. July 24, 1997). The costs of these studies alone could range from millions to hundreds of millions of dollars. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry*, 47 J. Health Econ. at 24. Those research and development costs would be in addition to the legal costs, the opportunity costs from diverting resources away from innovating new medicines, and the costs from withdrawing the medicine from the market while the specification changes are pursued.

Ultimately, allowing state law claims like Plaintiffs that second-guess FDA's expert evaluation and approval of drug specifications such as net weight range could prompt companies to redesign their manufacturing processes related to filling for FDA approval and hinder their ability to innovate new drug delivery systems.

C. Plaintiffs' Solution that Manufacturers Should Stop Selling Medications that Comply with FDA-Approved Specifications But Not Divergent State Requirements Harms Public Health.

Plaintiffs argue that federal law does not preempt their claims because Genentech could comply with their claims if it "limits its domestic sales to [vials] . . . containing at least 440 mg of the drug" and "discards or re-purposes" the FDA-approved vials that contain less than 440 mg. Opening Brief of Plaintiff-

Appellants at 50-51. Federal law should not permit any state law claim that requires manufacturers to throw away medicine that complies with all FDA-approved specifications.

Herceptin was the first therapy designed to specifically target the HER2 gene mutation that is associated with poor outcomes in breast cancer patients. Dias, et. al., *Human epidermal growth factor antagonists and cardiotoxicity-A short review of the problem and preventive measures*, 104 Critical Reviews in Oncology/Hematology at 43. The use of Herceptin, however, "changed the natural history of HER2 positive breast cancer" by reducing the risk of relapse by 50% and the risk of death by 33% for women with HER2-positive breast cancer. *Id.* Since FDA approved Herceptin for sale in 1998, it has become the standard of care for oncologists treating patients with early-stage HER2-positive breast cancer. M. Capelan, et. al., *Pertuzumab: a new hope for patients with HER2-positive breast cancer*, 24 Annals of Oncology 273, 273 (Aug. 21, 2012) ("[T]rastuzumab [the active ingredient of Herceptin] . . . has changed the approach to treat patients with HER2-positive BC and the prognosis of the disease.").

Plaintiffs' assertion that Genentech should have discarded all Herceptin vials that contained less than 440 mg recklessly jeopardizes the health of patients suffering from aggressive HER2-positive breast cancer. It does so in order to increase Medicare and insurance reimbursement for medical care providers. Plaintiffs' claims, which second-guess the net weight specification and

corresponding labeling FDA approved in the Herceptin BLA more than two decades ago, interfere with FDA's expert judgment on permissible net weights and harm public health.

CONCLUSION

FDA possesses the experience and expertise to effectively manage the inherent net weight variability in biologic medicines like Herceptin. Congress and FDA both understand "reasonable variations" in the quantity of medicine are essential due to the manufacturing and scientific complexities associated with weight fill. Permitting states to second-guess FDA's judgment about the proper net weight range for Herceptin undermines and poses an obstacle to the authority that Congress imparted to FDA and could reduce access to innovative medicines. This Court should affirm the judgment in favor of Genentech.

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Respectfully Submitted,

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This document complies with the type-volume limit of Federal Rule of Appellate Procedure 29(a)(5) because, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and 10th Circuit Rule 32(B), it contains 4,600 words.

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Dated: October 11, 2019

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Counsel hereby certifies that no privacy redactions were required to comply with Federal Rule of Appellate Procedure 25(a)(5) or Tenth Circuit Rule 25.5. Counsel also certifies that the hard copies submitted to the Court are copies of the ECF filing of October 11, 2019. Counsel further certifies that the ECF submission was scanned for viruses with the most recent version of a commercial virus scanning program, Trend OfficeScan XG, service pack 1 Build 5261, which was updated on October 11, 2019, and according to the program, is free of viruses.

Dated: October 11, 2019 /s/ K. Lee Marshall
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CERTIFICATE OF SERVICE

I hereby certify that on October 11, 2019, a copy of the Brief of *Amici Curiae* Pharmaceutical Research and Manufacturers of America, National Association of Manufacturers, and Biotechnology Innovation Organization was furnished through ECF electronic service to all counsel of record.

I further certify that seven (7) printed copies of the Brief of *Amici Curiae* Pharmaceutical Research and Manufacturers of America, National Association of Manufacturers, and Biotechnology Innovation Organization will be shipped via Federal Express to the Clerk, United States Court of Appeals for the Tenth Circuit, Byron White U.S. Courthouse, 1823 Stout Street, Denver, Colorado, 80257-1823, for delivery within two (2) business days of the below date.

Dated: October 11, 2019

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