IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS PHARMACEUTICALS CORPORATION, 59 Route 10 East Hanover, New Jersey 07936, *Plaintiff*, v. XAVIER BECERRA, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES, 200 Independence Avenue, S.W. Washington, DC 20201, and ROBERT M. CALIFF, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, 10903 New Hampshire Avenue, Silver Spring, MD 20993, *Defendants*.	Civil Action No. _____

VERIFIED COMPLAINT

Plaintiff Novartis Pharmaceuticals Corporation (Novartis) brings this Complaint against Defendants Xavier Becerra, in his official capacity as Secretary of Health and Human Services of the Department of Health and Human Services (HHS), and Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs, head of the Food and Drug Administration (FDA, or the agency), and alleges as follows:

PRELIMINARY STATEMENT

1. This is an action for temporary, preliminary, and permanent injunctive relief to set aside FDA's recent unlawful approval of a purported generic version of Novartis's drug product ENTRESTO® (sacubitril/valsartan).

2. ENTRESTO is a lifesaving therapy that reduces the risk of cardiovascular death and hospitalization in adult patients with chronic heart failure. Novartis has devoted substantial resources not only to researching and developing ENTRESTO, but also to implementing a free 12-month lifestyle and treatment support program for patients in order to combat the risks of untreated chronic heart failure.

3. On July 25, 2024, FDA published its approval of a purported generic version of ENTRESTO to be marketed by MSN Laboratories Private LTD (MSN). FDA's conduct in approving the purported generic product and denying two citizen petitions submitted by Novartis is unlawful for three separate reasons:

a. First, FDA has asserted that it may approve generic labeling that inappropriately rewrites ENTRESTO's approved indication and reverts to a superseded indication in an effort to avoid Novartis's patents. That position violates the governing statute, which requires the labeling to be "the same." It also violates FDA's implementing regulations, which provide that generic labeling may "omit" (that is, delete entirely) an indication that is subject to patent rights, but not add wording or make other changes to an indication remaining in the labeling.

b. Second, the labeling of MSN's purported generic product unlawfully deletes critical safety information contained in the ENTRESTO labeling. Under the agency's own regulations, FDA may not delete study information or other

instructions from the labeling of a generic drug product in order to avoid patent infringement if doing so would impact the safety or effectiveness of the resulting product.

c. And finally, in the citizen petition response, the agency has bound itself to approve generics that do not have identical active ingredients to ENTRESTO, as would be required to support approval of a generic drug. ENTRESTO has two active ingredients, sacubitril and valsartan, which exist in a specific and well-defined salt form, or chemical structure, in the finished drug product. FDA has taken the position that generic drug products do not need to have this same chemical structure, and instead may contain forms of ENTRESTO's active ingredients that are not present in ENTRESTO itself. That is unlawful.

4. For all of these reasons, FDA's denial of Novartis's citizen petitions and approval of MSN's product should be declared unlawful and set aside.

5. Time is of the essence in this case. MSN's approval permits MSN to flood the market at any moment, creating imminent and irreparable harm to Novartis. For that reason, Novartis plans to seek a temporary restraining order (TRO) enjoining the drug's approval and preventing the unlawful product from launching.

PARTIES

6. Plaintiff Novartis Pharmaceuticals Corporation is a corporation organized in Delaware with its principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

7. Defendant Xavier Becerra is the Secretary of HHS and is responsible for administering and enforcing the Food, Drug, and Cosmetic Act, 21 U.S.C. § 321, et seq.

Defendant Becerra maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20201.

8. Defendant Robert M. Califf, M.D., is the Commissioner of Food and Drugs and is responsible for supervising the activities of FDA, an administrative agency within HHS. Defendant Califf maintains an office at 10903 New Hampshire Avenue, Silver Spring, MD 20993.

JURISDICTION AND VENUE

9. Jurisdiction in this Court is grounded upon and proper under 28 U.S.C. § 1331, in that this civil action arises under the laws of the United States; 28 U.S.C. § 1346, in that this case involves claims against the federal government; 28 U.S.C. § 1361, in that this is an action to compel officers of the United States to perform their duty; and 28 U.S.C. §§ 2201–2202, in that there exists an actual justiciable controversy as to which Plaintiff requires a declaration of its rights by this Court and injunctive relief to prohibit Defendants from violating laws and regulations.

10. Venue is proper in this Court under 28 U.S.C. § 1391(b) and (e) because this is a civil action in which Defendants are officers of the United States acting in their official capacities and one of the Defendants maintains his office and conducts business in this judicial district.

FACTUAL BACKGROUND

1. Statutory and Regulatory Background

11. The Federal Food, Drug, and Cosmetic Act (FDCA) provides the statutory framework for FDA's regulatory oversight of drug products.

12. To gain approval to market a brand name drug, an innovator manufacturer can submit a full New Drug Application (NDA) under Section 505(b)(1) of the FDCA. 21 U.S.C. § 355(b)(1). An NDA contains reports of scientific studies conducted by or for the applicant, demonstrating that the drug is safe and effective. After a period of marketing exclusivity and expiration of any applicable patent rights, FDA may approve applications to market generic versions of the innovator drug, so long as they meet the criteria for approval.

13. Generic drugs are approved through an Abbreviated New Drug Application (ANDA) under Section 505(j) of the FDCA. 21 U.S.C. § 355(j). ANDAs generally do not include new clinical data. Instead, an ANDA relies on FDA's finding of safety and efficacy for a previously approved brand name drug, which is known as the "reference listed drug." In other words, the ANDA need not independently demonstrate safety or effectiveness; it need only establish that the generic product is equivalent to a reference listed drug already known to be safe and effective. *See* 21 U.S.C. § 355(j)(2).

14. To make this showing, an ANDA must demonstrate that the proposed generic is "pharmaceutically equivalent" to the reference listed drug (that is, contains the same active ingredient, in the same strength, dosage form, and route of administration); is labeled for the same uses as the reference drug; and is "bioequivalent" to the reference drug (that is, has the same rate and extent of absorption of the active ingredient(s) at the site of action). *See* 21 U.S.C. § 355(j)(2)(A).

15. In exchange for the ability to rely on clinical data for the reference listed drug, ANDA applicants must submit an appropriate patent certification or statement for each patent timely listed in the FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, colloquially known as the *Orange Book*. That process is driven in part by whether

the generic applicant intends to challenge the patent rights at issue. An ANDA applicant seeking approval for a use covered by a listed patent may challenge that patent by submitting a so-called "paragraph IV certification." *See* 21 U.S.C. § 355(b)(2)(A)(iv). Alternatively, an ANDA applicant may submit a "section viii" statement indicating that the applicant does not seek approval for the conditions of use claimed by the patent. *See* 21 U.S.C. § 355(j)(2)(A)(viii).

Same Labeling Requirement

16. The FDCA generally requires an ANDA applicant to demonstrate that its proposed labeling is the same as the labeling for the reference listed drug. 21 U.S.C. § 355(j)(2)(A). There are two limited exceptions to this principle: The ANDA labeling may differ from the labeling of the reference listed drug if those differences are due to (1) an approved suitability petition[1] authorizing certain changes from the reference listed drug that are not relevant here, or (2) the fact that the products are manufactured and distributed by different companies. 21 U.S.C. § 355(j)(2)(A)(v).

17. FDA has issued regulations addressing the "limited" nature of these exceptions to the same-labeling requirement. 54 Fed. Reg. at 28,884. In relevant part, FDA regulations provide that within the "different manufacturer[]" exception, the generic drug product may reflect labeling differences to address marketing exclusivity granted by FDA or patent rights but only so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7); 21 C.F.R. § 314.94(a)(8)(iv).

[1] A "suitability petition" is a petition to permit the filing of an ANDA for a drug that differs from the reference listed drug in certain respects not relevant in this case.

18. The agency also took the position that labeling differences designed to avoid patent protection or regulatory exclusivity must take the form of an ***omission*** of language, not the ***addition*** of language to current labeling:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers.
>
> Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or ***omission of an indication or other aspect of labeling protected by patent or accorded exclusivity*** under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

19. This rule is driven by the agency's position that if an ANDA applicant submits a section viii statement, it must omit from its labeling the use covered by the patent. FDA, *Application for FDA Approval to Market a New Drug*, 68 Fed. Reg. 36,676, 36,682 (Jun. 18, 2003) ("In determining whether an ANDA applicant can 'carve out' the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.").

20. The agency's regulations go beyond the plain text of the statute. But one thing the statute and regulations agree upon is that an ANDA applicant must demonstrate that its proposed labeling is the same as the *current* labeling for the reference listed drug. Both talk about "the labeling approved for the listed drug"—which clearly refers to the *current* approved labeling. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.127(a)(7); 21 C.F.R. § 314.94(a)(8)(iv). *See also* Ex. B (FDA Citizen Petition Response regarding Fanapt (iloperidone)) at 9 (noting that

in assessing labeling carve-outs, the agency must "start with the currently approved labeling" and that "earlier versions of the drug's labeling . . . have no relevance to this inquiry.") (internal footnote omitted); *see also* Docket No. FDA-2016-P-2654 (Nov. 28, 2016), *available at* https://www.regulations.gov/document/FDA-2016-P-2654-0008 (select "Petition Denial Letter").

Same Active Ingredient Requirement

21. The FDCA also requires that the generic drug product have the same active ingredient(s) as its reference listed drug. The statute provides:

> (I) if the listed drug . . . has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;
>
> (II) if the listed drug . . . has more than one active ingredient, information to show that ***the active ingredients of the new drug are the same as those of the listed drug***.

21 U.S.C. § 355(j)(2)(A)(ii) (emphasis added).

22. By regulation, FDA has defined "same as" for purposes of assessing ANDAs to mean, in relevant part, "identical in active ingredient(s)." 21 C.F.R. § 314.92(a)(1). FDA's regulations clarify that for purposes of assessing pharmaceutical equivalence, an "identical active drug ingredient" is "the same salt or ester of the same therapeutic moiety." 21 C.F.R. § 314.3(b) (definition of "pharmaceutical equivalents").

23. And as the agency has noted in rulemaking:

> The agency interprets the requirement that the active ingredients in the proposed drug product be the same as those of the listed drug to mean that the active ingredients must be identical. For example, if the proposed drug product contained a different salt or ester of the active ingredient in the listed drug, the active ingredient in the proposed drug product would not be identical to the active ingredient in the listed drug, and could not, therefore, be approved in an ANDA. ***Active ingredient in this context means the active ingredient in the finished drug product prior to its administration.***

Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,881 (July 10, 1989). FDA has made clear that differences in the chemical structure of an active ingredient render it a different active ingredient. As the agency has explained:

> FDA has long regarded chemical structure as being fundamental to the identity of an active ingredient. Consequently, FDA regards ***different salts and esters of the same therapeutic moiety as pharmaceutical alternatives*** rather than pharmaceutical equivalents. On the other hand, different polymorphs of an active ingredient that have the ***same primary chemical structure*** (the differences are in physical form) are considered pharmaceutical equivalents.

FDA Citizen Petition Response, Docket Nos. 00P-1550/CP1 and 01P-0428/CP1, at 28 (Feb.15, 2002) (Consolidated CP Response) (footnotes omitted) (emphases added).

24. FDA has long required generic drugs to have the same chemical structure as their reference listed product. *See* FDA, *Sameness Evaluations in an ANDA—Active Ingredients: Guidance for Industry* 4 (Nov. 2022), *available at* https://www.regulations.gov/docket/FDA-2022-D-0697/document. There, FDA confirmed:

> As part of the identity of an active ingredient, we generally consider the chemical form of an active ingredient to be the entire molecule, including those portions of the molecule that cause the drug to be an ester or salt. For the evaluation of sameness, the identity of the active ingredient may also encompass noncovalent derivatives (such as a complex, chelate, or clathrate, with some limitations described below) of the molecule as it exists in the drug product (i.e., in the finished dosage form). . . .
>
> The same active ingredient can exist in more than one physical form, such as polymorphs or co-crystals. Polymorphs are different crystalline forms of the same active ingredient; they differ in internal solid-state structure but not in chemical structure.

2. Novartis's ENTRESTO

25. ENTRESTO was approved by FDA in July 2015. ENTRESTO is currently approved to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Ex. A (ENTRESTO Labeling) § 1.1. It also has an approved pediatric indication. *Id.* § 1.2.

26. The approved indication for ENTRESTO has changed over time. To understand how and why, it's necessary to understand some background about heart function and heart failure. Heart failure is a complex clinical syndrome that affects millions of adults in the United States, and its prevalence is increasing. Studies estimate that it will eventually affect over 8 million adults by 2030.

27. Heart failure patients are sometimes classified by their left ventricular ejection fraction (LVEF), a widely used measure of heart pumping dysfunction. Ejection fraction is a measurement, expressed as a percentage, of how much blood the heart's left ventricle pumps out with each contraction. *See* American Heart Association, Ejection Fraction Heart Failure Measurement (last reviewed June 14, 2023), *available at* https://www.heart.org/en/health-topics/heart-failure/diagnosing-heart-failure/ejection-fraction-heart-failure-measurement.

28. When ENTRESTO was first approved in July 2015, it had an initial approved indication of reducing the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction (HFrEF). Ex. I (ENTRESTO Labeling); *see also* Ex. C (2015 FDA Clinical Review) at 29, 43. ENTRESTO's initial indication was based on the results of a clinical trial known as the PARADIGM-HF trial, which enrolled patients with heart failure and LVEF of *reduced* ejection fraction of *less than* or equal to 40%. *Id.* at 29.

29. In February 2021, FDA approved a supplement to ENTRESTO's NDA. Ex. D (2021 Supplemental Approval). The supplement was premised on the results of a second clinical trial, known as the PARAGON-HF trial, which enrolled patients with chronic heart failure and LVEF *greater than* or equal to 45%. Ex. F (Labeling Carve-Out Citizen Petition) at 7–8.

30. Based on the combined results of both trials, the ENTRESTO indication was expanded in February 2021 to include not only chronic heart failure patients with LVEF of less than or equal to 40%, but *also* those with LVEF greater than 40%, including those with preserved ejection fraction. As a result, ENTRESTO is now approved to treat *all* patients with chronic heart failure.

31. This approach reflects a modern and more sophisticated transition away from using LVEF as a strict criterion for classifying heart failure. Over time, research has shown that certain hallmarks of heart failure—including structural heart disease, a history of commonly reported symptoms, and objective signs—may not be strictly correlated with LVEF. *See* Biykem Bozkurt, et al., *Universal Definition and Classification of Heart Failure*, 23 Eur. J. Heart Failure 355 (2021). In fact, LVEF can vary by patient age and sex and may even change over time within the same heart failure patient—suggesting that a single threshold for "normal" ejection fraction should be resisted. *See* Carolyn Lam, et al., *Classification of Heart Failure According to Ejection Fraction*, 77 J. Am. Coll. Cardiology 3218–24 (2021). And certain heart failure patients with peculiar diagnostic profiles may be in a transitory phase between HFrEF and HFpEF; for these patients, LVEF is less likely to predict the likelihood of clinical benefit. *See* Davide Margonato, et al., *Heart Failure with Mid-range or Recovered Ejection Fraction: Differential Determinants of Transition*, Cardiac Failure Rev. (2020).

32. As FDA itself has noted, ENTRESTO's current labeling (1) reflects this new consensus by moving away from LVEF as a strict diagnostic criterion; and (2) recognizes that the universe of heart failure patients cannot be neatly sorted using the old LVEF-driven taxonomy. Officials at FDA's Center for Drug Evaluation and Research (CDER) have stated that "[t]he relationship between LVEF and treatment effect" that the agency had observed

"indicates a need to go beyond a dichotomous classification of HF based on a traditional LVEF cut-off." Charu Gandotra, et al., *Heart Failure Population with Therapeutic Response to Sacubitril/Valsartan, Spironolactone and Candesartan: FDA Perspective*, 56 Therapeutic Innovation & Regul. Sci. 7 (2022). The officials thus explained that because ENTRESTO confers a clinical benefit for some heart failure patients with LVEF that falls below normal levels, but still sits above the "traditionally used cut-off of 40 or 45%," FDA approved a new ENTRESTO label that does not turn on the LVEF cut-off, instead embracing other indicia of heart failure. *Id.*

33. Thus, ENTRESTO's labeling for adult patients now states: "ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in ***adult patients with chronic heart failure***. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat." Ex. A § 1.1 (emphasis added).

Modified Dosing Regimen Based on the TITRATION Study

34. Section 2.6 of the ENTRESTO labeling describes a modified dosing regimen for patients not taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB)—two drugs that increase blood flow by relaxing and widening blood vessels—or who were previously taking low doses of these agents prior to starting on ENTRESTO. *Id.* § 2.6. For the sake of brevity, such patients will be referred to herein as "ACE inhibitor or ARB naive patients."

35. Specifically, the ENTRESTO labeling directs physicians to initiate treatment for these patients with a reduced dose of ENTRESTO and then to up-titrate to the target dose over a greater number of titration steps more slowly than is used for other patients. *Id.*

36. This modified dosing regimen is derived from a clinical study known as the TITRATION study, which demonstrated that the dosing regimen in Section 2.6 of the ENTRESTO labeling resulted in fewer clinically relevant adverse events for this patient group and allowed them to reach the efficacious target dose. Ex. F at 24–26; Ex. H (Labeling Carve-Out Citizen Petition Response) at 40.

37. The modified dosing regimen studied in the TITRATION study had important safety implications for patients. Upon reviewing the TITRATION study, FDA concluded that "[a] longer titration period with a starting dose of 50 mg bid may reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an [ACE inhibitor] or ARB," as well as patients who are not currently taking an ACE inhibitor or ARB. Ex. C at 70.

38. The resulting modified dosing regimen is included in Section 2.6 of the ENTRESTO labeling, and states as follows:

> **2.6 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents**
>
> In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.
>
> Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

Ex. A § 2.6. This language in the FDA-approved labeling signals to patients and providers that the standard ENTRESTO dosing schedule could put ACE inhibitor or ARB-naïve patients at risk, and provides critical instructions that allows for safe administration of the drug to such patients. The labeling explicitly recognizes this modified dosing regimen should be used to mitigate risks for this patient population, and directs physicians and patients to initiate treatment with a reduced

dose of ENTRESTO and then to up-titrate to the target dose more slowly and over a greater number of titration steps than is used for other patients. *Id.* § 2.

39. Novartis is the owner of U.S. Patent No. 11,058,667 (the '667 Patent), which claims the modified dosing regimen for use in patients with heart failure with reduced ejection fraction. The '667 Patent issued on July 13, 2021, and expires on May 9, 2036.

40. In addition, Novartis timely owns three patents that cover methods of using sacubitril and valsartan in heart failure patients with preserved ejection fraction: U.S. Patent Nos. 9,517,226, 9,937,143, and 11,135,192.

41. These patents are listed in the *Orange Book*. Because of that patent protection, FDA is prohibited from approving generic labeling that references the protected uses until expiration of the relevant patent(s). 21 U.S.C. § 355(j)(5)(B)(ii)–(iii).

ENTRESTO's Active Ingredients

42. ENTRESTO is comprised of two active ingredients in a single chemical compound: sacubitril (which acts to block the action of neprilysin, thus preventing the breakdown of natriuretic peptides) and valsartan (which relaxes the blood vessels and lowers blood pressure). *See* Ex. A § 12.1.

43. Most combination drug products having two active ingredients contain physical mixtures of the two active ingredients. ENTRESTO is different. Its two active ingredients are not randomly mixed together; in fact, they are not mixed together at all. They are manufactured as a single compound and are present in the finished drug product as a single, contiguous chemical structure. Specifically, sacubitril and valsartan anions are bound together with sodium cations through hydrogen and ionic bonds to form a precisely defined salt complex. Ex. E (Same

Active Ingredient Citizen Petition) at 8–9. This structure is specifically called out in the FDA-approved labeling. Ex. A § 11.

44. FDA has acknowledged that this type of structure qualifies as a drug substance salt. FDA has defined "salt" to mean "an ionic or electrovalent crystalline compound." FDA, *Regulatory Classification of Pharmaceutical Co-Crystals: Guidance for Industry* 4 (Feb. 2018), *available at* https://www.fda.gov/media/81824/download. This describes ENTRESTO precisely. Ex. E at 1–4.

The Same Active Ingredient Citizen Petition

45. In April 2019, Novartis submitted a citizen petition to FDA explaining that any generic version of ENTRESTO must have the same active ingredients as ENTRESTO (the Same Active Ingredient Citizen Petition). *Id.* at 6–25. In that petition, Novartis noted that the chemical structure in which the two active ingredients appear in ENTRESTO must serve as the basis of establishing the sameness of the two products' active ingredients. *Id*. at 19–20.

46. Specifically, Novartis noted that the two active ingredients appear in ENTRESTO as a singular salt form (a valsartan-sacubitril-Na^+ complex), which defines the chemical structure of sacubitril and valsartan as they co-exist in the finished drug product prior to administration. *Id.* at 14. Novartis reminded FDA that its own framework for assessing sameness of active ingredients provides that the active ingredient of a drug product includes the specific salt or ester of the active ingredient present in the drug product. 54 Fed. Reg. at 28,881. And Novartis explained that the entire chemical structure of the salt form of the active ingredients present in ENTRESTO must serve as the basis of active ingredient sameness under FDA's established framework. *Id.* at 19–20.

47. For these reasons, Novartis requested that the agency require generic products that reference ENTRESTO to demonstrate active ingredient sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form of ENTRESTO, i.e., sacubitril and valsartan in ionic coordination with sodium with 1:1:3 stoichiometry. *Id.*

The Labeling Carve-Out Citizen Petition

48. In September 2022, Novartis submitted a citizen petition to FDA addressing the two labeling carve-out issues explained above (the Labeling Carve-Out Citizen Petition). Ex. F.[2] Novartis explained that it would be unlawful for FDA to revise the approved indication for purported generic versions of ENTRESTO by rewriting the indication to cover only patients with *reduced* ejection fraction.

49. Novartis noted that an ANDA indication statement that categorizes the patient population by reference to ejection fraction is inconsistent with the current ENTRESTO labeling, which reflects the agency's deliberate decision *not* to use ejection fraction as a strict diagnostic criterion to determine which patients may benefit from ENTRESTO. *Id.* at 3.

50. Novartis reminded the agency that generic applicants cannot reference discontinued labeling, such as the now-superseded ENTRESTO indication statement describing its use in patients with only "reduced ejection fraction." *Id.* at 20.

51. Novartis explained that it would be unlawful for FDA to approve generic drug products that contain the modified dosing regimen addressed in the TITRATION study and protected by the '667 Patent. *Id.* at 24–26.

[2] This petition was a resubmission of a substantially similar petition that Novartis filed in November 2021. FDA denied that prior petition without addressing its merits.

52. Novartis also explained that FDA was prohibited from carving the modified dosing regimen protected by the '667 Patent out from generic labeling because to do so would render the purported generic product less safe and effective than ENTRESTO for the remaining conditions of use. *Id.* at 24. Without the modified dosing regimen, patients with reduced ejection fraction who are ACE inhibitor or ARB-naïve, or who were previously taking a low dose of one of these agents before initiating ENTRESTO[3] would be administered the generic product under the standard titration schedule—including a higher starting dose and more rapid dosing regimen than that recommended for such patients. *Id.*

53. Novartis also documented the harms that would arise if FDA approved generic labeling that omitted the modified dosing regimen, explaining that such labeling would fail to inform patients and providers of the safest option for administering the drug to heart failure patients with reduced ejection fraction who are ACE inhibitor or ARB-naïve. *Id.* at 24–26.

3. FDA's Approval Of MSN Product And Denial Of The Citizen Petitions

54. On May 28, 2024, FDA denied Novartis's first citizen petition, which addressed the "same active ingredient" requirement. Ex. G (Same Active Ingredient Citizen Petition Response). Specifically, the agency rejected the argument that the same active ingredient requirement should be based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form—that is, sacubitril and valsartan in ionic coordination with sodium with 1:1:3 stoichiometry. *Id.* at 18–21.

55. The agency asserted that "there is no systemic exposure to the Entresto co-crystal, which disassociates in vivo to sacubitril and valsartan as stated in Entresto's labeling. Absent a

[3] For the sake of brevity, such patients will be referred to herein as "ACE inhibitor or ARB naive patients."

showing that the physical form of the Entresto co-crystal impacts the safe or effective use of the drug, FDA generally expects generic applicants to demonstrate 'sameness' based on the identity of the individual active ingredients (sacubitril sodium and valsartan disodium) of Entresto." *Id.* at 19.

56. FDA also took the position that "[u]nlike what we would expect from a new single active ingredient in salt form, the adhesive forces between the two active ingredients comprising the Entresto co-crystal (i.e., the sodium salts of sacubitril and valsartan) are weak as well as non-covalent and non-ionic." *Id*.

57. On July 24, 2024, FDA denied Novartis's second citizen petition, addressing the labeling carve-out issues. Ex. H. In doing so, FDA asserted that it may approve generic labeling that not only omits an approved indication, but also revises (and adds new language to) an approved indication. *Id.* at 35–36. In addition, FDA took the position that it could lawfully approve generic labeling that omitted the modified dosing regimen in ENTRESTO's labeling. *Id*. at 39–42.

58. The next day, FDA updated the Orange Book to reflect its approval of MSN's ANDA referencing ENTRESTO.

4. FDA's Conduct is Unlawful.

59. FDA's conduct in denying the citizen petitions and approving the MSN product was unlawful.

60. Agency action violates the APA when it violates the agency's governing statute. *Utility Air Regulatory Grp. v. EPA*, 573 U.S. 302, 315 (2014); *Orion Rsrvs. Ltd. P'ship v. Salazar*, 553 F.3d 697, 703 (D.C. Cir. 2009).

61. Agency action also is unlawful when it violates the agency's own regulations. *National Env't Dev. Ass'n's Clean Air Project v. EPA*, 752 F.3d 999, 1009 (D.C. Cir. 2014); *United States Lines, Inc. v. Federal Maritime Comm'n*, 584 F.2d 519, 526 n.20 (D.C. Cir. 1978).

62. Agency action also violates the APA when it is arbitrary and capricious, lacks a logical basis, treats similarly situated entities differently, or deviates from agency precedent without giving a reasoned explanation. *See, e.g.*, *Dillmon v. National Transp. Safety Bd.*, 588 F.3d 1085, 1089–90 (D.C. Cir. 2009); *County Of Los Angeles v. Shalala*, 192 F.3d 1005, 1022 (D.C. Cir. 1999).

63. FDA's conduct here is unlawful, several times over.

Unlawful Labeling Carve-Outs

64. FDA acted unlawfully when it permitted two labeling carve-outs for the purported generic product.

65. First, in denying the second citizen petition and approving the purported generic product, FDA completely rewrote the approved indication for ENTRESTO, reverting to a previous indication that has been superseded by amendments to the labeling. That is unlawful under both the FDCA and FDA's own regulations. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.127(a)(7).

66. The statute does not expressly allow for labeling carve-outs. And while the agency promulgated regulations that purport to retain discretion in some circumstances to "carve-out" (that is, delete entirely) an indication that is subject to patent rights, the regulations do not permit the agency to add wording or make other changes to an indication remaining in the labeling.

67. FDA also acted unlawfully in carving out critical safety information relating to a modified dosing regimen. Ex. H at 39. Specifically, FDA has taken the position that it may approve an ANDA omitting the modified dosing regimen found in Section 2.6 of the ENTRESTO labeling, which is derived from the results of the TITRATION study conducted by Novartis. *Id.* at 39–42.

68. FDA regulations prohibit labeling "carve-outs" unless the omissions "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7). FDA's carve-outs violate that maxim here.

69. The protected dosing regimen in Section 2.6 of the ENTRESTO labeling provides clear directions for patients and providers so that ENTRESTO is administered at a safe dose and on a tolerable schedule to a group of patients who may otherwise fail to achieve the target dose. Ex. F at 26. Without this information, these patients will face an increased likelihood of experiencing clinically relevant adverse events. *Id.*

70. Given the relationship between adverse events and treatment adherence, it is critical that labeling directs providers and patients to initiate treatment in the safest and best-tolerated manner. *Id.* at 25–26. Requiring the modified dosing regimen to be present on the labeling therefore also helps to ensure that patients are receiving the full benefits of the drug therapy, in addition to reducing the risks of adverse events. *Id.* at 26.

71. Carving out the modified dosing regimen from the purported generic product's labeling thus renders the product less safe and effective than ENTRESTO.

Same Active Ingredient

72. FDA also acted unlawfully when it concluded that the generic drug products satisfy the FDCA's active ingredient "sameness" test.

73. The FDCA requires that an ANDA contain information demonstrating that its active ingredient is the "same as"—that is, "identical" to—the reference listed drug's active ingredient as it exists in the drug product (i.e., in the finished dosage form). 21 U.S.C. § 355(j)(2)(A)(ii).

74. In addressing sameness, the agency has long considered "those portions of the [active ingredient] that cause the drug to be an ester or a salt." FDA, *Sameness Evaluations in an ANDA—Active Ingredients: Guidance for Industry* 4 (Nov. 2022), *available at* https://www.regulations.gov/docket/FDA-2022-D-0697/document.

75. In ENTRESTO's active ingredient, the sodium cations coordinate with sacubitril and valsartan anions through ionic bonds to form a single chemical structure. Ex. E at 8. Because this is the chemical structure in which ENTRESTO's active ingredients exist in the finished drug product, generics must match it.

5. FDA's Actions Will Cause Concrete And Imminent Harm To Patients And Novartis.

76. Both Novartis and the patient population will be irreparably harmed unless FDA's approval of the ANDA is vacated.

77. FDA's approval of MSN's ANDA opens the door for the MSN to flood the market with its purported generic versions of ENTRESTO at any moment. It is well known in the pharmaceutical industry that generic drugs quickly replace branded products soon after their launch. *E.g.*, Henry Grabowski et al., *Continuing Trends In U.S. Brand-Name And Generic Price Competition*, 24 J. Med. Econ. 908–917 (2021); Richard G. Frank et al., *The Evolution Of Supply And Demand In Markets For Generic Drugs*, 99 Milbank Q. 828, 835 (2021).

78. As a result of state automatic-substitution laws and other market dynamics, the purported generic product's market entry would cause ENTRESTO to suffer a dramatic loss of sales in the weeks and months following generic entry.

79. The impact on Novartis would be commercially devastating. ENTRESTO is Novartis's best-selling drug. Through the end of 2023, ENTRESTO has generated more than $10.5 billion in cumulative net sales in the United States since its launch. In 2021, ENTRESTO generated $1.7 billion in sales in the United States. In 2022, that figure grew to approximately $2.4 billion. And in 2023, ENTRESTO produced more than $3 billion in U.S. sales. *Id.* Revenues from ENTRESTO account for more than 17% of Novartis's total U.S. revenues, help fund Novartis's operations, and permit the company to invest in promising new drugs—particularly those that address unmet needs.

80. Novartis will suffer other harms as well. Injuries or side effects caused by purported generic versions of ENTRESTO are likely to be unfairly attributed by physicians and patients to Novartis. And as the manufacturer of the reference listed drug, Novartis will be forced to expend time and resources documenting, investigating, and responding to patient concerns that arise from substitution of a purported generic product—even when the issue originates with a patient's use of a purported generic product, not ENTRESTO.

81. Because revenues from ENTRESTO form a critical part of Novartis's ability to fund research and development, unlawful entry of purported generic products would undermine Novartis's ability to invest generously in research and development. The harms resulting from this lost investment could not be remedied after the fact: Progress toward developing critical new therapies will have stalled, and Novartis will have been subjected to significant risk of

falling behind its competitors. And Novartis will have suffered permanent reputational injury and loss of goodwill, hampering its ability to effectively promote ENTRESTO in the future.

82. Even if FDA later withdraws the purported generic products' approvals, Novartis would be unable to regain its earlier position because the prescribing and usage patterns will have irreversibly shifted in response to the purported generic products that were subsequently withdrawn.

83. Novartis would also be unable to recoup its current share of ENTRESTO sales because cash-paying patients are unlikely to be willing to pay a higher price for ENTRESTO after they have come to expect a lower price for a purported generic alternative.

84. Approximately 600 Novartis sales associates support ENTRESTO in some capacity. If a purported generic product is unlawfully allowed to enter the market, Novartis would be forced to make difficult decisions regarding staffing and employee retention, in addition to hundreds more who serve in commercial account management, marketing, marketing analytics, sales operations, training, physician education, financial planning, contracting, and research and development roles. Novartis could not continue to employ all of the sales representatives that support ENTRESTO (currently the largest sales force at Novartis) and would thus need to implement significant restructuring.

85. Because different therapeutic areas require different competencies and have different marketplace dynamics, Novartis would be unable to simply redeploy these cardiovascular product-trained representatives in service of a product approved for a different disease state. And because the respective salesforces for Novartis's other products in the cardiovascular space are optimally sized, the company would be unable to reassign the vast majority of its existing ENTRESTO salesforce to one of those products. Once lost, these

resources cannot be regained. Even if the purported generic drugs are later removed from the market, by that point Novartis's sales personnel will likely have moved on to other employment.

86. Unlawful entry of these purported generic products also will fundamentally affect Novartis's relationships with distributors and payers, undermine goodwill, and jeopardize key customer relationships.

87. There is no mechanism by which Novartis can be made whole for the injury that would result from the entry into the marketplace of MSN's unlawful purported generic product. And because the foregoing losses never can be recovered, Novartis will be irreparably harmed unless FDA's conduct is enjoined promptly.

88. The harm will not be limited to Novartis. Patients will also suffer irreparable harm absent injunctive relief. The FDCA requires sameness of active ingredients and labeling for a reason: The ANDA approval process is built on the premise that the safety and effectiveness of the brand name drug can supply the basis for approving an ANDA due to the sameness of the products to each other. *See* 21 U.S.C. § 355(j)(2)(A)(ii). If two products are not, in fact, the same, the agency's bridging between them is unwarranted.

89. In addition, patients are put at risk by omission of the modified dosing regimen from the labeling of the purported generic product. If the dose modification information were omitted from these purported generic versions of ENTRESTO, ACE inhibitor and ARB-naïve heart failure patients would receive treatment according to the standard adult heart failure dosing recommendations and would be titrated up more quickly than is tolerable, which would jeopardize their safety and result in heightened health risks for those required to discontinue treatment—all of which would have been potentially preventable under the current approved labeling for ENTRESTO. Ex. F at 25, 27–29.

90. The purported generic product also will generate physician and patient confusion. Patients and physicians often do not know when their brand-name ENTRESTO prescriptions have been substituted out for a purported generic version by the pharmacist—particularly in states with automatic-substitution laws. This resulting marketplace confusion and uncertainty will harm physicians, who rely on labeling information when prescribing drugs, as well as patients living with heart failure. These harms are impossible to remedy after the fact.

91. Because the ANDA approval clears the path for generic launch at any moment, these harms are imminent.

92. Conversely, neither FDA nor MSN will suffer any significant hardship if approval of MSN's ANDA is enjoined. MSN will simply be required to comply with the statute and regulations governing generic drug approvals.

93. The intent of Congress will be served by an Order directing FDA to rescind or stay its approval of the ANDA. In addition, such an Order will serve the public interest by protecting patient safety, and requiring FDA to comply with its obligations.

94. Providers and patients typically do not distinguish between harms caused by brand name drugs and generics based on them. Any injuries or fatalities resulting from the misuse of the purported generic product will be unfairly imputed to ENTRESTO, which would lead to reputational harm for the product and possibly to Novartis. These adverse effects on business reputation, goodwill, and relationships with physicians and patients constitute irreparable harm sufficient to warrant injunctive relief.

COUNT I
(Administrative Procedure Act, 5 U.S.C. §§ 700, *et seq.*)

95. Novartis realleges, reasserts, and incorporates by reference herein each of the foregoing allegations as though set forth fully herein.

96. FDA's approval of the MSN ANDA and denial of Novartis's Citizen Petitions was unlawful and in violation of the FDCA and the agency's own regulations, policies, and procedures.

97. FDA's approval of the MSN ANDA and denial of Novartis's Citizen Petitions constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

98. FDA's approval of the MSN ANDA and denial of Novartis's Citizen Petitions was not based on a reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

99. FDA's approval of the MSN ANDA and denial of Novartis's Citizen Petitions constitutes final agency action for which Novartis has no other adequate remedy within the meaning of 5 U.S.C. § 704.

100. Both Novartis and the patient population will be irreparably harmed unless FDA's approval of the MSN ANDA is vacated.

101. There is no mechanism by which Novartis can be made whole for the injury that would result from the entry into the marketplace of an unlawful MSN product. Novartis is without an adequate remedy at law because of the unique nature of the harm.

102. The intent of Congress will be served by an Order directing FDA to withdraw its approval of the MSN ANDA. In addition, the public interest will be served by such an Order.

PRAYER FOR RELIEF

For the foregoing reasons, Novartis prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that FDA's approval of MSN's ANDA and denial of the Citizen Petitions was unlawful;

B. An order vacating and setting aside FDA's approval of MSN's ANDA and

denials of the Citizen Petitions;

C. Temporary, preliminary, and permanent injunctive relief vacating FDA's approval of MSN's ANDA and denials of the Citizen Petitions and enjoining launch of the MSN product;

D. An order awarding Novartis its costs, expenses, and attorneys' fees incurred in these proceedings pursuant to 28 U.S.C. § 2412; and

E. Such other and further relief as the Court deems just and proper.

Respectfully submitted,

/s/ Catherine E. Stetson
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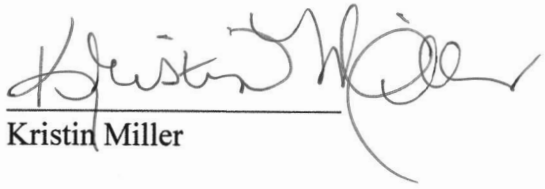
Dated: July 30, 2024

VERIFICATION

I, the undersigned, having read the allegations of the foregoing Verified Complaint, hereby declare under penalty of perjury and pursuant to 28 U.S.C. § 1746 that the factual allegations asserted in the Verified Complaint are true and correct.

Executed this 30th day of July, 2024.



Kristin Miller