IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS PHARMACEUTICALS CORPORATION, *Plaintiff*, v. XAVIER BECERRA, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES, and ROBERT M. CALIFF, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, *Defendants*.	Civil Action No. _____

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF NOVARTIS'S MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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INTRODUCTION

This case represents a sharp departure from FDA's statutory and regulatory mandate to require that a generic drug be the "same" as its reference listed drug. Generic manufacturers are permitted to rely upon clinical studies performed on the brand name products on which they are based. But to do so, they must first establish that their products are the "same" as those brand name products in a number of key respects. The sameness requirements play a critical role in public health by ensuring that generic drug products are just as safe and effective as their brand-name counterparts. When FDA fails to enforce these statutory and regulatory requirements, the agency runs afoul of its governing statute. It also increases risks to patients and harms drug manufacturers who have invested heavily in developing important new therapies. That is what has occurred here.

On July 25, 2024, FDA publicly announced its approval of an application by MSN Laboratories Private LTD (MSN) seeking to market a purported generic version of Novartis's drug product ENTRESTO® (sacubitril/valsartan). It did so in violation of the agency's governing statute and regulations, as well as its own past practices and processes. First, FDA unlawfully revised the approved indication for the purported generic drug product, violating both statutory and regulatory requirements. And second, in order to approve the purported generic product, FDA unlawfully carved out critical safety information conveying a modified dosing regimen for use in certain vulnerable patient populations, in violation of its own regulations. Each of these failures independently renders the agency's decision unlawful, and invalidates the agency's approval of the MSN product.

The unlawfully approved MSN product is poised to flood the market at any moment. Once it does, it will quickly take over the market, decimating ENTRESTO's sales and causing Novartis

immediate and devastating losses. These losses will threaten Novartis's ability to continue critical patient education and access programs, undermine its ability to invest generously in research and development for other critical pipeline drug products, and jeopardize Novartis's relationships with physicians, patients, insurers, and distributors.

Novartis therefore requests a TRO and/or preliminary injunction staying FDA's approval of the ANDA as soon as possible, and in any event by **August 8, 2024**.

STATEMENT OF FACTS

A. Statutory and Regulatory Background

Drug Approval Process

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

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 effectiveness 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 "the same as" a reference listed drug already known to be safe and effective. *See* 21 U.S.C. § 355(j)(2). To make this showing, an ANDA must demonstrate that the proposed

generic is "pharmaceutical[ly] 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 conditions of use 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).

In exchange for the ability to rely on the 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

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 only if those differences are due to a suitability petition[1] or the fact that the products are manufactured and distributed by different companies. 21 U.S.C. § 355(j)(2)(A)(v).

[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.

FDA has issued regulations addressing the limited exceptions to the same-labeling requirement, and recognizing that Congress intended the exceptions to be narrowly drawn. 54 Fed. Reg. at 28,884 ("FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited."). In relevant part, FDA regulations provide that within the "different manufacturer[]" exception, the generic drug product may reflect labeling differences to address marketing exclusivity 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).

In those same regulations, 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). This rule is driven by the agency's related 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.").

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 at 9 (FDA Citizen Petition Response regarding Fanapt (iloperidone), Docket No. FDA-2016-P-2654 (Nov. 28, 2016) (Fanapt Petition Response) (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), *available at* https://www.regulations.gov/document/FDA-2016-P-2654-0008 (select "Petition Denial Letter").

B. Novartis's ENTRESTO

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.*

Heart failure is a complex clinical syndrome that affects millions of adults in the United States, and its prevalence is increasing. Verified Compl. ¶ 26. Studies estimate that it will eventually affect over 8 million adults by 2030. *Id.* Heart failure patients are sometimes classified by their left ventricular ejection fraction (LVEF), a 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.

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 § 1.1. 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 with *reduced* ejection fraction of *less than* or equal to 40%. Ex. C (2015 FDA Clinical Review).

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. 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 reduced ejection fraction (that is, LVEF of less than or equal to 40%), but also those with LVEF greater than 40%, including those with preserved ejection fraction (that is, the ejection fraction is 50% or higher at diagnosis) (HFpEF). *Id.* at 2–3. As a result, ENTRESTO is now approved to treat *all* patients with chronic heart failure, whether classified as having reduced ejection fraction or not. *Id.* at 22.

This approach reflects a modern and more sophisticated understanding of heart failure, in which the medical community has transitioned 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).

As FDA itself has noted, ENTRESTO's current labeling (1) reflects this new more advanced 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 HFrEF/HFpEF taxonomy. Ex. F at 3. Officials at FDA's Center for Drug Evaluation and Research (CDER) have noted 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 noted 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%" for HFrEF, FDA approved a new

ENTRESTO label that does not turn on the HFrEF/HFpEF distinction, instead embracing other indicia of heart failure. *Id.*

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).

The TITRATION Study

Section 2.6 of the current 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 before starting on ENTRESTO.[2] Ex. A § 2.6. Specifically, the labeling directs physicians and such patients to initiate treatment 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.*

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. The modified dosing regimen studied in the TITRATION study had important safety implications for patients. Upon reviewing the TITRATION study, FDA concluded that "the

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

benefits of [ENTRESTO] outweigh the risks. . . . We believe the key risks of hypotension, renal impairment, hyperkalemia, and angioedema can be adequately managed through clinical monitoring and dose titration," finding "[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.[3]

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

[3] Hypotension is low blood pressure. Renal impairment is kidney impairment. Hyperkalemia refers to excess potassium in the blood.

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.

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. Miller Decl. ¶ 4. 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. These patents are listed in FDA's *Orange Book*. Because of that patent protection, FDA is prohibited from approving generic labeling that references the patented use until the expiration of the relevant patent if a generic applicant does not challenge this patent or does not prevail in such a challenge. 21 U.S.C. § 355(j)(5)(B)(ii)-(iii).

C. The Labeling Carve-Out Citizen Petition

In September 2022, Novartis submitted a citizen petition to FDA (the "Labeling Carve-Out Citizen Petition"). Ex. F.

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. 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. 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; *see also supra* at 6.

The Labeling Carve-Out Citizen Petition raised another labeling carve-out issue as well. Novartis noted that the agency was prohibited from approving generic drug products that contain the modified dosing regimen addressed in the TITRATION study and protected by the '667 Patent. Ex. F at 3. Novartis also explained that FDA was prohibited from carving the modified dosing regimen out from generic labeling because to do so would be to 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 naive would be administered the generic product under the standard titration schedule in the labeling—including a higher starting dose and more rapid dosing regimen than that recommended for such patients. *Id.* Novartis documented the harms that would arise if FDA approved a generic label that omitted the modified dosing regimen, explaining that such a 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 naive. *Id.*

D. FDA's Approval of The Purported Generic And Denial of the Citizen Petition

On July 24, 2024, FDA denied Novartis's Labeling Carve-Out Citizen Petition. Ex. H. In doing so, FDA asserted that notwithstanding its regulation, it retains the authority to 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 omits the modified dosing regimen in ENTRESTO's labeling. *Id*. at 39–42. The next day, FDA updated the Orange Book to reflect its approval of an ANDA submitted by MSN identifying Entresto as the reference listed drug.

E. FDA's Actions Will Cause Immediate, Irreparable Harm

FDA's actions pose a substantial and imminent harm to both Novartis and patients. FDA's approval of the purported generic MSN product opens the door for MSN to flood the market with its product immediately. Miller Decl. ¶ 9. It is well known in the pharmaceutical industry that generic drugs quickly replace branded products in the marketplace 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); *Collagenex Pharms., Inc. v. Thompson*, No. CIV.A. 03-1405(RMC), 2003 WL 21697344, at *10 (D.D.C. July 22, 2003) ("rapid erosion of branded drug sales can occur when a generic enters the market"); *In re Relafen Antitrust Litig.*, 218 F.R.D. 337, 344 (D. Mass. 2003) ("A generic drug typically enters the market at a price substantially below that of a branded drug. For this reason, the generic drug quickly captures a large market share.").

As a result of state automatic-substitution laws and other market dynamics, the purported generic product's premature launch is projected to cause ENTRESTO to suffer a dramatic loss of sales in the weeks and months following generic entry. Miller Decl. ¶ 9. The impact on Novartis would be commercially devastating. ENTRESTO is Novartis's best-selling drug. In 2023, revenues from ENTRESTO were more than $3 billion, accounting for approximately 17% of Novartis's total U.S. revenues. *Id.* ¶¶ 6, 37. These revenues help fund Novartis's operations, and permit the company to invest in promising new drugs—particularly those that address unmet needs. *Id.* ¶ 33. Novartis will also suffer reputational harm if patient suffer adverse events as a result of the unlawful labeling carve-outs. That is because physicians and patients are often not aware which product a patient is taking as a result of automatic substitution. *Id.* ¶ 39.

Even if this Court or FDA later withdraws the purported generic product's approval, Novartis would be unable to regain the strength of its earlier position because the market will have irreversibly shifted. For one, it is difficult to remove generic products from the marketplace after they have been sold to distributors and wholesalers and delivered to pharmacies. *Id.* ¶ 38. Customer expectations will have shifted in response to the generic pricing. And Novartis will also suffer ongoing loss of goodwill among physicians and patients after they have become used to a lower priced purported generic product.

ARGUMENT

To secure a TRO or preliminary injunction, a movant must establish (1) "that he is likely to succeed on the merits," (2) "that he is likely to suffer irreparable harm in the absence of preliminary relief," (3) "that the balance of equities tips in his favor," and (4) "that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008); *see also Council on Am.-Islamic Relations v. Gaubatz*, 667 F. Supp. 2d 67, 74 (D.D.C. 2009) ("The standard for obtaining injunctive relief through either a temporary restraining order or a preliminary injunction is well established.").

These four factors all strongly favor granting the requested relief here.

I. NOVARTIS IS LIKELY TO PREVAIL ON THE MERITS.

The APA requires a reviewing court to "hold unlawful and set aside agency action, findings, and conclusions" that are determined to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Agency action must be set aside as unlawful when it violates a statute, *Orion Rsrvs. Ltd. P'ship v. Salazar*, 553 F.3d 697, 703 (D.C. Cir. 2009), or the agency's own regulation, *National Env't Dev. Ass'n's Clean Air Project v. EPA*, 752 F.3d 999, 1009 (D.C. Cir. 2014). Agency action is arbitrary and capricious when it treats similar cases differently without adequate explanation. *See, e.g.*, *Lone Mountain Processing, Inc.*

v. Secretary of Labor, 709 F.3d 1161, 1164 (D.C. Cir. 2013). Agency conduct also violates the APA where it defies logic and reflects a want of reasoned decisionmaking. *See, e.g.*, *Fox v. Clinton*, 684 F.3d 67, 80 (D.C. Cir. 2012) (holding agency action "arbitrary and capricious for want of reasoned decisionmaking").

Judicial review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987). "Courts need not and under the APA may not defer to an agency interpretation of the law simply because a statute is ambiguous." *Loper Bright Enters. v. Raimondo*, 144 S. Ct. 2244, 2273 (2024). The reviewing court may defer to an agency's technical or scientific judgments to the extent they are consistent and reasonable, but the court does "not hear cases merely to rubber stamp agency actions. To play that role would be tantamount to abdicating the judiciary's responsibility under the Administrative Procedure Act." *Natural Res. Def. Council, Inc. v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000) (internal quotation marks omitted).

FDA violates all of these maxims here.

A. The Purported Generic Product Does Not Have the Same Approved Indication As ENTRESTO.

The FDCA requires that a proposed generic product show that the "labeling proposed for the new drug is the same as the labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(A)(v). This includes the approved indication. *See* 21 U.S.C. § 355(j)(2)(A)(vi); 21 U.S.C. § 355(b)(1)(A)(i). The ANDA labeling may differ from the labeling of the reference listed drug only if those differences are due to (i) an approved suitability petition; or (ii) the fact that the products are manufactured and distributed by different companies. 21 U.S.C. § 355(j)(2)(A)(v).

FDA violated that statutory requirement here. ENTRESTO is indicated for all patients with heart failure, regardless of their ejection fraction. Ex. A § 1.1; Ex. F at 22. And yet, for the

MSN product, FDA has *rewritten* the approved indication to cover only patients with *reduced* ejection fraction, essentially reverting to the now-superseded ENTRESTO labeling that FDA approved back in 2015. Ex. H at 39–42.

In doing so, the agency appears to ignore its own conclusion in 2021 that ENTRESTO's labeling should be changed to reflect essential new information regarding the safety and efficacy of ENTRESTO in treating an expanded set of patients. Ex. D. In revising the indication in 2021, FDA eliminated the previous reference to "reduced ejection fraction," and added two statements to the indication, both of which emphasize the importance of taking a patient's LVEF into consideration:

- "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal," and
- "LVEF is a variable measure, so use clinical judgment in deciding whom to treat."

Ex. A § 1.1.

But when describing the indicated patient population, FDA affirmatively decided to eschew a quantitative measure of ejection fraction. It did so in order to ensure that the drug could be used more broadly, for *all* heart failure patients, regardless of their ejection fraction results. As revised, ENTRESTO's labeling now reads: "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." *Id.*

In denying Novartis's citizen petition, FDA jettisoned that approach for generic applicants. The agency previewed an "illustrative example" of permissible labeling for generic versions of ENTRESTO, as follows: "ENTRESTO is indicated to reduce the risk of cardiovascular death and

hospitalization for heart failure in adult patients with chronic heart failure **and reduced ejection fraction**. Left ventricular ejection fraction (LVEF) is a variable measure, so use clinical judgment in deciding whom to treat." Ex. H at 33–34 (emphasis in original).

FDA's decision to rewrite the approved indication for generic products is unlawful, for several independent reasons.

1. The Generic Labeling Violates The FDCA By Reverting To A Superseded ENTRESTO Indication.

First, the generic labeling endorsed by FDA is unlawful because it violates the plain text of the FDCA, which requires generic labeling to match the *current* labeling for the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(v). Despite FDA's protestations to the contrary, the generic labeling blessed by the agency essentially reverts to the original (now superseded) indication for ENTRESTO by once more confining its use to the reduced ejection fraction population. Ex. H at 39–42. But ENTRESTO's indication statement has evolved since FDA first approved the drug, and clinical trial data now supports use of the product in an expanded patient population. Ex. F at 14–16.

The statutory text is unmistakably framed in the present condition: Both the statute and FDA's implementing regulations require sameness to "the labeling approved for the listed drug." 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). "Same as the labeling approved for the listed drug" does not connote a comparison between a generic drug's new labeling and a reference drug's old labeling: It means the generic drug must be compared to what the reference listed drug's labeling says *now*. The FDCA's same-labeling requirement does not entertain throwbacks to old labeling. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 614 (2011) (statute requires "generic drug's label to match its brand-name counterpart's") (noting that if the reference listed drug's labeling changes, so too must the generic product's). This statutory command is clear

and the Court must apply its meaning, without any deference to FDA. *Loper Bright*, 144 S. Ct at 2273.

The statutory structure and surrounding context confirm the text's plain meaning. *See Deal v. United States*, 508 U.S. 129, 132 (1993) (observing the "fundamental principle of statutory construction (and, indeed, of language itself) that the meaning of a word cannot be determined in isolation, but must be drawn from the context in which it is used"). The same-labeling requirement is qualified by two exceptions: The statute exempts labeling differences required because the generic product was approved under a suitability petition or "because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). That's it. Under the FDCA, unless one of these two exceptions applies, a generic product label must match the reference listed drug's label to a T. Because neither exemption excuses compliance with the law here, the statutory same-labeling requirement is directly operative on any purported generic that seeks to rely on ENTRESTO.

For that reason, the agency has noted that an ANDA applicant must demonstrate that its proposed labeling is the same as the *current* labeling for the reference listed drug. Ex. B 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") (footnote omitted). And FDA has recognized that after the agency expands an indication statement through a new sNDA approval, the drug's prior labeling has been superseded. *Cf. AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 81 n.16 (D.D.C. 2012) (sNDA approval letter "stated that previous labeling supplements have been superseded by this approval action") (internal quotation marks omitted).

ENTRESTO's 2015 label has been discontinued in light of new information demonstrating advanced understanding of the drug's efficacy and safety, and it thus cannot serve as the basis for a purported generic hoping to rely on its approval in 2024. Put simply, it is 2024, not 2015. A generic may omit an indication, but it cannot rewind the clock and rewrite the indication as it once was.

2. The Generic Labeling Violates the FDCA and FDA's Regulations By Adding New Language Rather Than Merely Omitting Language.

The generic labeling also is unlawful because it violates the statutory requirement that the indications be "the same," 21 U.S.C. § 355(j)(2)(A), and the agency's own regulations, which permit "*omission* of an indication" to address a marketing exclusivity or patent right, but not a rewriting of the reference product's current approved indication. 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

Agencies must comply with their governing statutes. *Orion Rsrvs. Ltd. P'ship*, 553 F.3d at 703. In addition, "[a] precept which lies at the foundation of the modern administrative state is that agencies must abide by their rules and regulations." *Reuters Ltd. v. FCC*, 781 F.2d 946, 947 (D.C. Cir. 1986). *See also International Exps., Inc. v. Mattis*, 265 F. Supp. 3d 35, 50 (D.D.C. 2017) ("[I]t is elementary that an agency must adhere to its own rules and regulations.") (quoting *Secretary of Labor, Mine Safety & Health Admin. v. Western Fuels-Utah, Inc.*, 900 F.2d 318, 325 (D.C. Cir. 1990)).

The FDCA requires that the labeling for an approved generic be the "same" as the labeling for the reference listed product. 21 U.S.C. § 355(j)(2)(A). There are only two limited exceptions to this principle: The ANDA labeling may differ from the labeling of the reference listed drug only if those differences are due to a suitability petition or the fact that the products are "produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). 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. And by its plain text, the "different manufacturer" exception would permit differences in generic labeling to identify a different manufacturer, product name, or company address. Neither of these exceptions is applicable here. For that reason alone, the agency's position violates the plain language of its governing statute.

FDA's actions also violate its implementing regulations. By regulation, FDA has explained its views on the limited exceptions to the same-labeling requirement. 54 Fed. Reg. at 28,884 ("FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited."). In relevant part, FDA regulations provide that within the "different manufacturer" exception, the generic drug product may reflect a labeling carve-out to address marketing exclusivity granted by FDA or patent rights 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). With regard to carving out approved indications, FDA's regulation is clear that only a specific type of revision is permitted: an "*omission of an indication* or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F)." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

The regulation goes well beyond the plain statutory text, which is problematic for FDA's position that it can carve out any indications at all. But even if the regulation were valid, the agency has violated it here. The word "omission" has a clear meaning: It means to leave something out. *See* Merriam-Webster Dictionary (defining "omission" as "something left out"); Britannica Dictionary (defining "omission" as "the act of not including or doing something"); Cambridge Dictionary (defining "omit" as "to fail to include or do something").

This means that omitting (i.e., deleting) an approved indication is permissible, but rewriting one is not. When a drug has been approved for multiple indications but a generic has been approved for just one of those indications, FDA takes the position that it may permit the generic manufacturer to market its product without the labeling for the reference listed drug's other indications. *See Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996). But when—as here—a reference drug's labeling has just one indication statement, FDA cannot allow a generic manufacturer to *rewrite* the portions of the single-indication labeling at will. There is no reasonable interpretation of the word "omission" to permit the revision of language to modify the current indication to reflect something different.

3. FDA's Conduct Is Arbitrary And Capricious.

FDA's actions also are arbitrary and capricious in violation of the APA. FDA has failed to explain how a full cloth rewriting of the reference drug's labeling is consistent with the rest of the ENTRESTO labeling.

As described, ENTRESTO's current labeling indicates that it is approved for the broad use to treat chronic heart failure, and is not limited to use in patient populations with specific, quantified ejection fraction metrics. Ex. A § 1.1. As a result of this non-quantitative indication, the current labeling also offers additional guidance to physicians to use their "clinical judgment" in making prescribing decisions. *Id.*

The labeling for the purported generic drug product represents a departure from this comprehensive approach to chronic heart failure treatment and a return to the now-outdated strictly quantitative approach that FDA itself rejected in favor of ENTRESTO's current labeling. Ex. F at 5–8. Those changes, and the data upon which those changes were based, were approved by FDA

as an accurate representation of ENTRESTO's appropriate treatment indication. The agency has provided no cogent reason to backtrack from the currently approved non-quantitative indication.

B. MSN's Labeling Impermissibly Carves Out Critical Safety Information.

FDA acted unlawfully in another respect as well: by permitting the generic labeling to omit critical safety information relating to a modified dosing regimen.

As noted above, the FDCA requires that a proposed generic product show that the "labeling proposed for the new drug is the same as the labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(A)(v). Under the agency's own implementing regulations, a generic drug product may include a labeling carve-out to address statutory marketing exclusivity or patent rights—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).

The FDA-approved labeling for the MSN product, however, carved out critical safety information relating to a modified dosing regimen derived from the results of Novartis's TITRATION study, which demonstrated that the modified dosing regimen results in fewer clinically relevant adverse events for this patient group and allowed a greater proportion of these patients to reach the efficacious target dose. Ex. F at 24–26; Ex. H at 40. Upon reviewing the TITRATION study, FDA concluded that "the benefits of LCZ696 outweigh the risks . . . We believe the key risks of hypotension, renal impairment, hyperkalemia, and angioedema can be adequately managed through clinical monitoring and dose titration," finding "[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 12, 70.[4]

In concluding the TITRATION findings should be incorporated into the FDA-approved ENTRESTO labeling, the agency stated that "[t]he results of the phase 2 dose regimen study (TITRATION) suggests that patients who were previously on low dose of ACEi and ARBs might benefit from a slow up-titration regimen (a 6-week regimen) rather than a fast up-titration regimen (a 3-week regimen) to increase tolerability and reduce the risk of adverse events such as hypotension, hyperkalemia and renal impairment. ***We agree with the proposed titration strategy from a safety perspective.***" *Id.* at 70 (emphasis added).

Lest there be any doubt about the agency's findings on safety, the modified dosing regimen is included in the labeling as a mandatory requirement, not a suggestion to healthcare providers. When FDA recommends modified dosing, the labeling will say "recommend." It did not do so here. Section 2.6 of the ENTRESTO labeling 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)]*.

[4] Hypotension is low blood pressure. Renal impairment is kidney impairment. Hyperkalemia refers to excess potassium in the blood.

Ex. A § 2.6. This language signals to patients and providers that the standard ENTRESTO dosing schedule provided in the labeling 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 over a greater number of titration steps than is used for other patients. *Id.* § 2.6.

In denying Novartis's citizen petition, however, FDA determined that the modified dosing regimen from Section 2.6 in the ENTRESTO labeling may be omitted in order to avoid coming into conflict with one of Novartis's patents. Ex. H at 39–42. In doing so, FDA violated its own regulations, which permit this type of carve-out only if it does not undermine the generic drug's safety or effectiveness. 21 C.F.R. § 314.94(a)(8)(iv); 21 C.F.R. § 314.127(a)(7).

The labeling carveout that FDA approved in order to get around Novartis's patent renders the resulting generic product both less safe and less effective. 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. A § 2.6. There are no other warnings on the ENTRESTO labeling that warn prescribers that patients previously taking low doses of ACE inhibitors/ARBs, or patients who have never taken those drugs, as a group are particularly vulnerable to potential adverse events. *Id.* And although other warnings in the ENTRESTO labeling address dosing adjustments for patients already experiencing hypotension, renal dysfunction, and hyperkalemia, they do not direct providers on how to initiate treatment with

sacubitril and valsartan or titrate to the recommended maintenance dose. *Id.* That is inconsistent with the agency's treatment of ENTRESTO.

No need to take our word for it; FDA has said as much. 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.

The modified dosing instructions impact efficacy too. The modified dosing regimen helps to ensure that patients are receiving the full benefits of the drug therapy, not just reducing the risks of adverse events. Ex. F at 26. The improved safety and tolerability imparted by the titration regimen allows patients who may previously have discontinued much-needed therapy to continue to benefit from ENTRESTO's proven effectiveness. Miller Decl. ¶ 8.

Now FDA wants to pull this back: While the modified dosing regimen "might" be beneficial to ACE/ARB naïve patients, the agency asserts that there is no need for such patients to receive the "safest and best-tolerated option." Ex. H at 41. Aside from the fact that patients and their providers would likely disagree, that is not the standard spelled out in the agency's regulations. Those regulations very clearly—and correctly—require that the generic drug's labeling be no "*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) (emphasis added). The agency's citizen petition response ignores this standard, suggesting that the safety profile of the MSN generic need not match the safety profile of ENTRESTO. Agencies are not permitted to change the plain meaning of their regulations like that on the fly.

FDA has no response to these points, other than to argue that "[e]ven without the protected section 2.6 modified dosing regimen, section 5 of Entresto's prescribing information . . . describes sufficiently how health care providers can manage intolerability or adverse reactions for all patients initiating and up-titrating on Entresto." Ex. H at 41. That position is exactly backwards from a safety perspective, and wholly inconsistent with the agency's actions at the time it approved ENTRESTO's labeling. FDA's regulations require labeling for modified dosing when necessary, including titration regimens in specific patient populations intended to reduce the risks of adverse reactions. *See* 21 CFR 201.57.57(c)(3); *see also* FDA Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products—Content and Format Guidance for Industry, Revision 1 (2023). In determining the modified dosing regimen should be included in the labeling, FDA found that regimen improved the safety profile of ENTRESTO for these patients. Ex. C at 70 ("We agree with the proposed titration strategy from a safety perspective.").

There is an obvious and critical difference between *preventing* an adverse event from occurring (Section 2.6) and letting patients suffer a potentially preventable adverse event and then advising on how to treat it. Nothing in Section 5 suggests to physicians that the ARB/ACE naive patients would be at particular risk of these adverse events. Patients now may face the known risk of being administered MSN's product without the benefit of labeling that FDA considered at the time to be necessary for the safe use of ENTRESTO in patients and face potentially preventable adverse events as a result. That approach inverts the very rationale of the modified dosing regimen, which is to prevent at-risk patients from experiencing an adverse event and maximize their chances of reaching the target dose for safe and effective treatment. At minimum, FDA failed to adequately consider this important problem, and its actions are unlawful on that basis alone.

II. NOVARTIS WILL SUFFER IRREPARABLE HARM ABSENT A TRO.

Novartis will suffer irreparable harm absent immediate judicial intervention. Novartis is the beneficiary of statutory rights of patent and market exclusivity, "specifically intended by Congress" at that. *Mylan Labs. Ltd. v. FDA*, 910 F. Supp. 2d 299, 313 (D.D.C. 2012). It is well settled that irreparable harm is inflicted when an agency denies statutory rights or benefits. *See, e.g.*, *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 1, 11 (D.D.C. 2008) (loss of a "clear statutory entitlement . . . may be sufficiently irreparable to justify emergency injunctive relief"); *Apotex, Inc. v. FDA*, No. CIV.A. 06-0627 JDB, 2006 WL 1030151, at *17 (D.D.C. Apr. 19, 2006) ("Once the statutory entitlement has been lost, it cannot be recaptured."); *Kyne v. Leedom*, 148 F. Supp. 597, 601 (D.D.C. 1956) (loss of a "statutory right" "works irreparable harm"). Yet that is what FDA has done here. By permitting unlawful labeling carve-outs, FDA has done an end-run around Novartis' patent rights and statutory exclusivities.

In addition, Novartis projects that ENTRESTO would experience a dramatic loss of sales in the weeks and months following generic entry. Miller Decl. ¶ 9. This is consistent with broader industry trends showing that branded products lose between 85-90% of their market volume within the first three months of generic entry. *Id.* While serious economic injury on its own is rarely enough to show irreparable injury, *see Wisconsin Gas. Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985), "courts have found irreparable harm where the movant has made a strong showing that the economic loss would significantly damage its business above and beyond a simple diminution in profits," *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 43 (D.D.C. 2000).

Because its safety and effectiveness profile has improved the lives of so many patients, ENTRESTO has become Novartis's best-selling drug product, accounting for approximately 17% of Novartis's total U.S. revenues. Miller Decl. ¶ 37. The drug has generated more than $10.5 billion in total net sales in the United States since its launch and more than $3 billion in 2023

alone—with sales projected to climb in the coming years to meet the needs of an aging population and growing prevalence of heart failure diagnoses. *Id.* ¶¶ 6, 7. Without immediate relief, Novartis will suffer a rapid reduction in its sales, and the amount that payers are willing to pay for ENTRESTO will crater. *Id.* ¶ 19. These injuries cannot be undone: "Courts have recognized that price erosion and diminished sales can constitute irreparable harm." *Bayer HealthCare, LLC v. FDA*, 942 F. Supp. 2d 17, 26 (D.D.C. 2013).

If Novartis loses its statutory exclusivity, it will suffer significant economic losses, which can never be recouped from FDA (or any other actor) due to sovereign immunity. *See, e.g.*, *Clarke v. Office of Fed. Hous. Enter. Oversight*, 355 F. Supp. 2d 56, 65–66 (D.D.C. 2004) (holding that economic losses constitute irreparable injury where they are unrecoverable due to government immunity); *Xiaomi Corp. v. Department of Def.*, No. CV 21-280 (RC), 2021 WL 950144, at *10 (D.D.C. Mar. 12, 2021) (collecting cases). And even if the unlawful generic entry were enjoined at some later date, Novartis would never be able to regain ENTRESTO's market position. ENTRESTO is the number one treatment for heart failure prescribed by cardiologists today, but the purported generic's entry would upend this position: Physicians tend to prescribe lower tier drugs and/or grant patients' requests for them—especially generic drugs, which are viewed to be both (a) interchangeable for the brand name product and (b) cheaper. Miller Decl. ¶ 21.

Once a purported generic version of ENTRESTO enters the market, pharmacists will have either the option or often the obligation (depending on state law) to fill prescriptions written for either "ENTRESTO" or "sacubitril/valsartan" with the generic product—except in those rare cases when the physician writes "Dispense As Written" or "Brand Medically Necessary" on the prescription or the patient refuses to consent to the substitution. *Id.* ¶ 17. Pharmacies, where the overwhelming majority of ENTRESTO prescriptions are filled, are also incentivized to fill the

prescription with the generic product whenever possible, to maximize the reimbursement spread. *Id.* ¶ 18.

Unlawful entry of the purported generic product also will fundamentally affect Novartis's relationship with distributors and payers, undermine goodwill, and jeopardize key customer relationships. *Id.* ¶ 39. There is no mechanism by which Novartis can be made whole for the injury that would result from the entry into the marketplace of the unlawful purported generic drug. *Id.* And because the foregoing losses never can be recovered from FDA, Novartis will be irreparably harmed unless FDA's conduct is enjoined promptly. *Id.* ¶ 37.

ENTRESTO enjoys favorable positions on both commercial payers' and Medicare Part D's lists of approved prescription drugs, known as formularies. *Id.* ¶ 21. Upon entry of the purported generic, Novartis expects that insurers would place those products on their preferred tiers and drop ENTRESTO from their formularies entirely. *Id.* This would lead to immediate and substantial loss of sales. *Id.* ¶ 23.

For all these reasons, even if the purported generic product is later withdrawn, the prescribing and usage patterns will have irreversibly shifted. *Id.* ¶ 27. This Court recently observed that where "[t]he nature of [a market] is . . . such that users are unlikely to return to platforms that they have abandoned," injurious regulatory action results in irreparable harm when the company "would not be able to recover the harm to its user base" even if the action were "later held to be unlawful." *TikTok Inc. v. Trump*, 490 F. Supp. 3d 73, 84 (D.D.C. 2020).

Without temporary relief, Novartis also will suffer reputational harm and an irretrievable loss of goodwill among patients, physicians, and other players within the cardiovascular health space. *Id.* ¶ 39. Reputational injury in the form of lost goodwill is also irreparable injury. *Bayer HealthCare*, 942 F. Supp. 2d at 26. *See also Morgan Stanley DW Inc. v. Rothe*, 150 F. Supp. 2d

67, 77 (D.D.C. 2001) (loss of "customer trust and goodwill" constituted irreparable harm). Injuries or side effects caused by purported generic version of ENTRESTO containing unsafe labeling are likely to be unfairly attributed by physicians and patients to Novartis. Miller Decl. ¶ 40. 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. *Id.* ¶ 43.

Novartis's investment in research and development will be harmed if the purported generic product is permitted to unlawfully enter the market. Because revenues from ENTRESTO are a critical part of Novartis's ability to develop new therapies that treat critical health conditions, *id.*, the "loss of research and development funding as a result of [a generic's] entry into the market" will be irreparable, *Bayer HealthCare*, 942 F. Supp. 2d at 26. By way of example, Novartis plans to continue its expansion into the cardiovascular marketplace with LEQVIO, an FDA-approved cholesterol-lowering drug, and pelacarsen, a drug currently in development to reduce lipoprotein(a). Miller Decl. ¶ 37. If an unlawful generic enters the market, all of these important activities would be jeopardized, prolonging the conduct of clinical studies and/or eliminating the company's ability to fund certain programs to advance patient care. *Id.* 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. *Id.* ¶ 33. And Novartis will have suffered permanent reputational injury and loss of goodwill, hampering its ability to effectively promote ENTRESTO in the future. *Id.* ¶ 36.

If the purported generic product is unlawfully allowed to enter the market, Novartis also would be forced to make difficult personnel decisions that would affect hundreds of Novartis employees responsible for supporting ENTRESTO in some capacity. *Id.* ¶ 30. Novartis will be forced to initiate significant restructuring within the company, including within its sales force. *Id.* 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. *Id.* ¶ 31.

III. THE BALANCE OF EQUITIES FAVORS GRANTING A TRO.

The balance of equities also tips sharply in favor of the requested relief. Neither FDA nor any third party has a legitimate interest in taking action that is contrary to law, as "[t]here is generally no public interest in the perpetuation of unlawful agency action." *League of Women Voters of United States v. Newby*, 838 F.3d 1, 12 (D.C. Cir. 2016). This principle favors preliminary relief when balancing the equities.

Novartis has demonstrated an immediate need for judicial relief. Temporary injunctive relief also will benefit FDA by keeping it within the bounds of the law. It will benefit any generic filers that stayed within the statutory and regulatory bounds, by creating an even playing field. It will benefit the generic approval process going forward by clarifying the standard governing ANDA approvals, so all parties can plan accordingly. And it will benefit the public by fulfilling the statutory scheme that Congress designed to serve the public interest.

There is no irreparable harm on the other side of the ledger: A TRO that preserves the status quo harms no one. FDA would suffer no consequence if the TRO were granted, as it has no stake in the matter other than complying with the law. And MSN has not launched its products at this stage. As a result, absolutely nothing will change for MSN in the short term if a TRO is granted. Indeed, that is "the primary purpose of" temporary injunctive relief: "to preserve the

object of the controversy in its then existing condition—to preserve the status quo." *Aamer v. Obama*, 742 F.3d 1023, 1043 (D.C. Cir. 2014) (quoting *Doeskin Products, Inc. v. United Paper Co.*, 195 F.2d 356, 358 (7th Cir. 1952)). But while the harm to generic manufacturers is non-existent, the countervailing harm to Novartis is enormous.

IV. GRANTING A TRO WOULD PROTECT THE PUBLIC INTEREST.

Finally, an injunction here would serve the public interest. The public has an unmistakable interest in seeing that laws are faithfully executed by public officials. *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("there is a strong public interest in meticulous compliance with the law by public officials"); *see also, e.g.*, *O'Donnell Constr. Co. v. District of Columbia*, 963 F.2d 420, 429 (D.C. Cir. 1992); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998) (district court properly concluded public interest in "faithful application of the laws" favored granting preliminary relief); *Newby*, 838 F.3d at 12 (there is "a substantial public interest in having governmental agencies abide by the federal laws that govern their existence and operations") (cleaned up).

Patients will also suffer irreparable harm absent injunctive relief. Physicians will mistakenly assume that ENTRESTO may not be prescribed for heart failure patients with preserved ejection fraction, and these patients will miss out on life saving therapies. *See* Miller Decl. ¶¶ 39, 40. And if the dose modification information were omitted from purported generic versions of ENTRESTO, patients who are not currently taking ACE inhibitor or ARB, or who are taking low doses of those drugs, 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, reduce their likelihood of reaching the target dose shown to be effective, and result in heightened health risks for those required to discontinue treatment—all of

which would have been potentially preventable under the current approved label for ENTRESTO. *See* Ex. A.

Patients and physicians will rarely 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. Miller Decl. ¶ 39. 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. *Id.* ¶ 40. These harms are impossible to remedy after the fact.

Further, if the purported generic product is allowed to unlawfully enter the market, the anticipated precipitous drop in prescriptions and revenue may threaten the company's ability to continue to fund critical support programs that are collectively expected to assist more than 200,000 patients in 2024. *Id.* ¶ 35.

There is a keen public interest in ensuring that the statutory and regulatory regime governing drug approvals is not sidestepped. That interest assumes heightened importance in this case, where holding FDA to its statutory and regulatory obligations "is consistent with the FDA's mission and is in the public interest." *Bracco*, 963 F. Supp. at 30. A TRO would advance that interest by issuing relief "[t]hat will assure that the FDA meets its statutory obligations." *Id.*

CONCLUSION

For the foregoing reasons, Novartis's motion for a TRO and/or preliminary injunction should be granted.

Respectfully submitted,

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