

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS PHARMACEUTICALS
CORPORATION,

Plaintiff,

v.

XAVIER BECERRA, *et al.*,

Defendants.

and

MSN PHARMACEUTICALS INC., *et al.*,

Intervenor-Defendants.

No. 24-cv-02234 (DLF)

MEMORANDUM OPINION

Novartis Pharmaceuticals Corporation brings this action against the Secretary of Health and Human Services and the Commissioner of the Food and Drug Administration (“FDA”) for injunctive relief. Novartis alleges that FDA violated the Administrative Procedure Act, the Federal Food, Drug, and Cosmetic Act, and the agency’s implementing regulations by approving an application by intervenor-defendants MSN Pharmaceuticals Inc. and MSN Laboratories Private Ltd. (collectively, “MSN”) to market a generic version of Novartis’s heart failure drug Entresto. Before the Court is the plaintiff’s Motion for Summary Judgment, Dkt. 38, and the federal and intervenor-defendants’ Cross Motions for Summary Judgment, Dkts. 43, 46. For the reasons that follow, the Court will deny the plaintiff’s motion and grant the defendants’ motions.

I. BACKGROUND

A. Statutory Background

The Federal Food, Drug, and Cosmetic Act provides the statutory framework for FDA’s oversight of drug products. Manufacturers must obtain FDA approval to market a new drug by submitting a New Drug Application containing clinical data from studies demonstrating the drug is safe and effective. 21 U.S.C. § 355(b)(1). The original manufacturer often holds multiple patents covering the drug product as well as patented methods-of-use of the drug. FDA maintains a publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations* (colloquially, the “Orange Book”), listing active drug patents including method patents. After the exclusivity period expires for a patented drug product, generic manufacturers may submit an Abbreviated New Drug Application (“ANDA”) to obtain FDA approval to market a generic version of the drug. 21 U.S.C. § 355(j). ANDAs need not include independent clinical data of the drug’s safety or effectiveness; the applicant need only establish its generic is “the same as” a previously approved reference drug. *See id.* § 355(j)(2).

To demonstrate “same”-ness, an ANDA applicant must show its generic drug has the same labeling and the same active ingredients as the reference drug, among other requirements. *Id.* § 355(j)(2)(A)(ii), (v). If the applicant seeks approval for a drug with uses protected by patents listed in the Orange Book, the applicant may file a “Section viii statement” certifying it will not market or label the generic for patented-protected uses. *Id.* § 355(j)(2)(A)(viii). Section viii permits applicants to carve out protected uses—resulting in a so-called “skinny-label”—subject to statutory and regulatory constraints. *See Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405–06 (2012) (noting that Section viii skinny-label carveouts were intended to “speed the introduction of low-cost generic drugs to market”). To accommodate Section viii applicants, the Federal Food, Drug, and Cosmetic Act provides an exception to same-labeling requirements for

“changes required . . . because the [generic] drug and the [reference] drug are produced or distributed by different manufacturers.” 21 U.S.C. § 355(j)(2)(A)(v).

FDA regulations further define same-labeling requirements. 21 C.F.R. § 314.94(a)(8)(iv). Regulations reiterate that a generic may differ from the reference label if the drug is produced by a “different manufacturer[],” to account for differences in marketing exclusivity or patent rights:

[D]ifferences 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.

Id. (emphasis added); *see also id.* § 314.127(a)(7) (permitting approval of “changes required because . . . aspects of the [reference] drug’s labeling are protected by patent”). However, the labeling differences may “not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.” *Id.*

FDA regulations also provide that a generic must be “identical in active ingredient(s)” to the reference drug. 21 C.F.R. § 314.92(a)(1); *see* 21 U.S.C. § 355(j)(2)(A)(ii). An active ingredient is “any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.” 21 C.F.R. § 314.3(b) (definition of “Active ingredient”). Regulations further define an “identical active drug ingredient” as being “the same salt¹ . . . of the same therapeutic moiety.” *Id.* (definition of “Pharmaceutical

¹ A salt is a chemical compound comprised of an anion (a negatively-charged atom or group of atoms) and a cation (a positively-charged atom or group), linked by an ionic bond. *See* FDA Opp’n at 30–31, Dkt. 44; FDA, *Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals* at 4 (Feb. 2018) (“Salts: Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal”).

equivalents”). An “[a]ctive moiety” is “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be . . . [a] salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex . . .) . . . responsible for the physiological or pharmacological action of the drug substance.” *Id.* (definition of “Active moiety”). Active ingredient sameness is evaluated based on the chemical structure of the drug’s finished dosage form, prior to administration. 54 Fed. Reg. 28,872, 28,881 (July 10, 1989); *see also* FDA, *Sameness Evaluations in an ANDA – Active Ingredients, Guidance for Industry* at 4 (Nov. 2022) (“[W]e 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.”). But drug ingredients need not have the same solid state physical form to have the same chemical identity. *See Final Rule: Abbreviated New Drug Application Regulations*, 57 Fed. Reg. 17,950, 17,958–59 (Apr. 28, 1992) (active ingredient sameness does not require finding that “solid state forms of the drug have not been altered”).

B. Factual Background

In 2015, FDA approved Novartis’s chronic heart failure medication Entresto. *See generally* AR 11–55, Dkt. 54. Three aspects of Entresto’s labeling and formulation are relevant to this dispute—the label’s indication statement encompassing all adult chronic failure patients; the label’s description of a certain dosing regimen; and the chemical identity of Entresto’s active ingredients.

1. Entresto Indication

The indication statement on Entresto’s label states the drug is approved to treat chronic heart failure in all adult patients. Chronic heart failure patients are sometimes classified by a diagnostic criterion called left ventricular ejection fraction (LVEF)—the ability of the left heart ventricle to pump out blood with each contraction. *See* Compl. Ex. I § 14, Dkt. 1-9; AR 3920.

Normal LVEF ranges from 52 to 72 percent in men and 54 to 74 percent in women, and below-normal measurements indicate the heart is not contracting properly. AR 3920. Patients with lower LVEF measurements may suffer from a more severe form of chronic heart failure. AR 3935. Novartis initially sought approval for Entresto relying on the results of a clinical trial (the “PARADIGM” trial) enrolling only reduced ejection fraction patients, with LVEF at or below 35 percent. *Id.* 3923–24. PARADIGM established Entresto’s safety and effectiveness for that patient population, so the drug’s original label reflected that it was only indicated to treat reduced ejection fraction patients, *see* AR 19:

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction.

After Entresto’s approval, Novartis completed another clinical trial (the “PARAGON” trial) to evaluate the drug’s effectiveness for *preserved* ejection fraction patients, with LVEF at or above 45 percent. AR 3964–66. PARAGON demonstrated that preserved ejection fraction patients also benefitted from Entresto, albeit less so than reduced ejection fraction patients. AR 3964–65. Intervening medical research also revealed that certain hallmarks of heart failure may not be strictly correlated with LVEF, and the medical community has transitioned away from LVEF as a strict diagnostic criterion. *See* Novartis Mem. at 8, Dkt. 39; AR 4638–41. In 2021, FDA approved a supplement to Entresto’s indication reflecting that the drug benefits chronic heart failure patients broadly, beyond reduced ejection fraction patients. The supplement also added language, based on extrinsic research, suggesting Entresto “may not be effective at the upper range of LVEF” and cautioning prescribers to use clinical judgment “because LVEF is a variable measure.” AR 3940, 4013–14. That indication, in effect today, 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.

Entresto Label § 1.1, Compl. Ex. A, Dkt. 1-1. Novartis owns three Orange Book-listed method patents—Patent Nos. 9,517,226; 9,937,143; and 11,135,192 (the “Indication Patents”)—that presumptively cover the use of Entresto to treat the preserved ejection fraction patient population. *See* Novartis Mem. at 12.

2. *Entresto Dosing Regimen*

Entresto’s label provides a modified dosing regimen to reduce risks for patients not already taking high doses of angiotensin-converting enzyme inhibitors (“ACE inhibitors”) or angiotensin II receptor blockers (“ARBs”)—two drugs with similar effects on the circulatory system as Entresto. AR 1471. Based on a clinical study known as TITRATION, Novartis determined that introducing Entresto more slowly to patients new to or taking only low doses of ACE inhibitors and ARBs resulted in moderately fewer adverse side effects. *Id.* 300–2. The study compared two dosing regimens: (1) a condensed regimen, with patients initially receiving 100mg of Entresto twice daily increased to 200mg over 2 weeks; and (2) a conservative regimen, with patients initially receiving 50mg of Entresto twice daily increased to 200mg over 2 weeks. AR 3925. The TITRATION results showed that the latter regimen resulted in moderately fewer patients suffering the clinically adverse side effects of hypotension, renal impairment, and hyperkalemia. *See* AR 302. The TITRATION findings are reflected in Section 2.6 of the Entresto label, which recommends a lower starting dose and longer titration period for the relevant patients. *Entresto Label* § 2.6. Section 2.6 is the only portion of Entresto’s label with dosage management instructions specific to that patient population. AR 4021. Section 5 of the label provides more

generalized “Warnings and Precautions,” and it advises prescribers that a reduced initial dose of Entresto may mitigate risks of hypotension, renal impairment and hyperkalemia for all patients. *See Entresto Label* § 5.3–5.5.

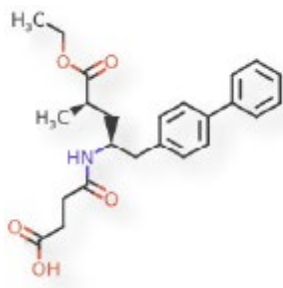
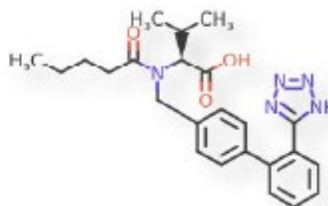
During clinical review, FDA determined that the Section 2.6 dosing regimen “seem[ed] reasonable” and that a “longer titration period with a [lower] starting dose . . . *may* reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an [ACE inhibitor] or ARB.” AR 301 (emphasis added). The agency also determined, however, that TITRATION showed “[Entresto] was well tolerated . . . following either a condensed or conservative [dosing] regimen[.],” AR 3925, and that “[a]vailable evidence does not suggest that the safety profile of [Entresto] would be significantly different between [ACE inhibitor]/ARB naive patients and [ACE inhibitor]/ARB experienced patients.” AR 310. Patent No. 11,058,667 (the “Dosage Patent”) presumptively covers the Section 2.6 dosing regimen. *See* Novartis Mem. at 12.

3. *Entresto Active Ingredients*

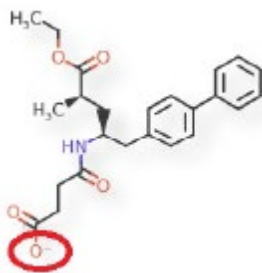
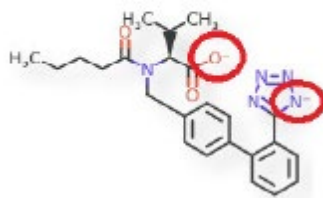
Entresto has two active ingredients—derivatives of sacubitril and valsartan. AR 1477. “Sacubitril” and “valsartan,” pictured below,² refer to the protonated acid forms of the compounds—that is, the neutral-charge forms where no dissociable hydrogen atoms³ have been removed or replaced with different cations. *See* FDA Opp’n at 28–31, Dkt. 44.

² *See* FDA & National Center for Advancing Translational Sciences, *Global Substance Registration System – Sacubitril* (last visited May 24, 2024); FDA & National Center for Advancing Translational Sciences, *Global Substance Registration System – Valsartan* (last visited May 23, 2024).

³ A “dissociable hydrogen atom” is a hydrogen atom within a molecular compound that easily separates (or “dissociates”) when the compound is dissolved in a solvent like water. Dissociation leaves the resultant compound with a net negative charge. *See* FDA Opp’n at 30–31.

**Sacubitril****Valsartan**

The protonated acid forms are the “active moiety[ies]” of the drug, responsible for its “physiological or pharmacological action.” FDA Opp’n at 30; 21 C.F.R. § 314.3(b). “Sacubitril anion” and “valsartan anion” refer to the compounds’ negative-charged forms, after dissociable hydrogen atoms are removed (pictured below, removals circled). FDA Opp’n at 31.

**Sacubitril Anion** (–1 charge)**Valsartan Anion** (–2 charge)

Negatively-charged anions may form “ionic bonds”—linkages resulting from the electrostatic attraction between oppositely charged ions—with positively-charged cations (for example sodium, Na⁺). An ionically-bonded compound is a salt. *See Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals* at 4. As relevant here, a sacubitril anion ionically bound to one sodium cation is “sacubitril sodium” salt, and a valsartan anion ionically bound to two sodium cations is “valsartan disodium” salt. AR 2784–86.

FDA explains that ions may also form linkages that are weaker than ionic bonds. For example, a “co-crystal” is a lattice structure formed from two or more chemically distinct compounds, in a fixed ratio, linked by nonionic (and noncovalent) bonds. *See Guidance for*

Industry: Regulatory Classification of Pharmaceutical Co-Crystals at 4 (co-crystals are “composed of two or more different molecules, one of which is the [active ingredient], in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds”). Compounds linked into co-crystal form are understood to retain distinct chemical identities, as inter-compound linkages are weak relative to intra-compound ionic (or covalent) bonds. *Id.* at 2.

The Entresto label states that the drug product is a “complex⁴ comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively.” AR 1476. FDA characterizes the complex as a [REDACTED]

[REDACTED]. See AR 58, 810–11. [REDACTED]

[REDACTED] See 810–11 ([REDACTED])

[REDACTED]); *id.* 58 (noting that “structural X-ray diffraction” and “spectroscopic characterization” data support the finding that the Entresto complex is a co-crystal rather than a salt); *id.* 2801 (describing Entresto as a “co-crystal” of “the sodium salts of sacubitril and valsartan”).

⁴ A “complex” is “a molecular entity formed by loose association involving two or more molecular entities (ionic or neutral); bonding is normally noncovalent.” AR 58; *see also* Complex, *International Union of Pure and Applied Chemistry Compendium of Chemical Terminology* (3d ed. 2019) (“IUPAC Gold Book”).

⁵ A “hydrate” co-crystal is a lattice structure that incorporates water molecules. *See* FDA Opp’n at 32. The parties do not dispute that hydration is a solid state physical attribute that does not affect active ingredient sameness. *See id.* at 37; Novartis Reply at 13, Dkt. 50.

4. *MSN's ANDA for Generic Sacubitril/Valsartan*

MSN submitted its ANDA for generic sacubitril and valsartan tablets in 2019. AR 1688. To avoid infringing Novartis's Indication and Dosage patents, MSN filed a Section viii statement and modified its generic label to omit those patented methods. *Id.* 1689. MSN's generic label carves out the treatment of adult preserved ejection fraction patients from its indication statement:

<i>Entresto Label § 1.1</i>	<i>Generic Label § 1.1, Dkt. 13-1 (modifications emphasized)</i>
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.	Sacubitril and valsartan tablets are indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure <u>and reduced ejection fraction</u> . ~~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.	<u>Left ventricular ejection fraction (LVEF)</u> is a variable measure, so use clinical judgment in deciding whom to treat.

MSN's label also carves out the dosing regimen for patients new to or taking low doses of ACE inhibitors and ARBs, by omitting Section 2.6 altogether:

<i>Entresto Label § 2.6</i>	<i>Generic Label §§ 2.4–2.7</i>
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 . . . to follow the recommended dose escalation thereafter.	N/A

The parties do not dispute that MSN's label otherwise complies with sameness requirements.

The active ingredients of MSN's generic are also derivatives of sacubitril and valsartan. Its tablets contain "anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3, respectively." *Generic Label* § 11. MSN's product contains sacubitril sodium salt and valsartan disodium salt. [REDACTED]

C. Administrative and Procedural History

In April 2019, Novartis submitted a citizen petition (the "Active Ingredient Petition") requesting FDA refrain from approving any Entresto-related ANDA for drugs not comprised of "one complex with coordinated ionic bonds between anionic sacubitril, anionic valsartan, and cationic sodium." AR 2812. It argued that the "two active ingredients" in Entresto appeared in a contiguous valsartan-sacubitril-sodium complex, and so a generic comprised of "a physical mixture of individual sodium salts" would violate active ingredient sameness requirements. AR 2812–13, *see* 21 C.F.R. § 314.92(a)(1); 21 U.S.C. § 355(j)(2)(A)(ii). In May 2024, in a 26-page letter, FDA denied the petition as inconsistent with its longstanding position that active ingredient sameness generally depends on the chemical "identity of [a drug's] individual active ingredients," rather than the ingredients' physical form (for example, as a co-crystal). AR 2800–03 & n.116. FDA explained that it "view[ed] [Entresto] as a fixed-combination" of its active ingredients—sacubitril sodium and valsartan disodium. AR 2801.

In September 2022, Novartis submitted another citizen petition (the "Labeling Petition") requesting that FDA refrain from approving ANDAs proposing the labeling carveouts challenged in this action. AR 3959–62. Novartis raised essentially the same arguments that it does in its summary judgment motion. *Id.* On July 24, 2024, FDA denied the petition in a 45-page letter

detailing why the carveouts would be proper under statute and regulation and would not risk the drug's safety or efficacy. *See generally* AR 2910–54. That same day, FDA approved MSN's ANDA No. 213748 for generic sacubitril and valsartan tablets. AR 1688–1691.

On July 30, 2024, Novartis filed suit to challenge the denial of Novartis's citizen petitions and the approval of MSN's ANDA. Compl. ¶¶ 1–4, Dkt. 1. Novartis alleges FDA's actions violate the APA; the Federal Food, Drug, and Cosmetic Act; and the agency's own regulations. *Id.* That same day, Novartis filed a motion for a temporary restraining order and/or preliminary injunction, to set aside the denial of the Labeling Petition and the approval of MSN's ANDA. Dkt. 3. With the parties' consent, the Court treated the motion as for a preliminary injunction. It denied the motion for lack of likelihood of irreparable harm to Novartis and committed to resolving the merits of this action within 60 days—by October 13, 2024. Mem. Op., Dkt. 23. Novartis appealed the denial of preliminary relief, and the D.C. Circuit granted an emergency stay of FDA's approval of the MSN generic. *See Novartis Pharms. Corp. v. Becerra*, No. 24-5186 (D.C. Cir.). The Court permitted MSN to intervene as defendant, and it granted the parties' joint motion for a protective order covering trade secret and other confidential information. Dkt. 36. Before the Court are the parties' cross-motions for summary judgment. Dkts. 38, 43, 46.

II. LEGAL STANDARDS

Under Rule 56 of the Federal Rules of Civil Procedure, summary judgment is appropriate if the moving party “shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.” Fed. R. Civ. P. 56(a); *see also Anderson v. Liberty Lobby Inc.*, 477 U.S. 242, 247–48 (1986). A “material” fact is one that could affect the outcome of the lawsuit. *See Liberty Lobby*, 477 U.S. at 248; *Holcomb v. Powell*, 433 F.3d 889, 895 (D.C.

Cir. 2006). A dispute is “genuine” if a reasonable jury could determine that the evidence warrants a verdict for the nonmoving party. *See Liberty Lobby*, 477 U.S. at 248; *Holcomb*, 433 F.3d at 895.

In an Administrative Procedure Act case, summary judgment “serves as the mechanism for deciding, as a matter of law, whether the agency action is supported by the administrative record and otherwise consistent with the APA standard of review.” *Sierra Club v. Mainella*, 459 F. Supp. 2d 76, 90 (D.D.C. 2006). The Court will “hold unlawful and set aside” agency action that is “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” 5 U.S.C. § 706(2)(A). Agency action is “not in accordance with law,” *id.*, if the agency violates statutory restrictions, *e.g.*, *United States v. Fla. E. Coast Ry. Co.*, 410 U.S. 224, 235–36 (1973). In evaluating an agency’s interpretation of a statute, “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). Rather, the Court must “exercise independent judgment” in construing the statute. *Lake Region Healthcare Corp. v. Becerra*, 113 F.4th 1002, 1007 (D.C. Cir. 2024) (citation omitted). Agencies must also follow their own regulations. *Reuters Ltd. v. FCC*, 781 F.2d 946, 947 (D.C. Cir. 1986). “An agency’s interpretation of its own regulations is entitled to judicial deference,” unless that interpretation is “plainly erroneous or inconsistent with the regulation.” *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 763 (D.C. Cir. 2010) (citation omitted).

In assessing an agency’s factfinding and its policy judgments under § 706, the Court cannot “substitute its judgment for that of the agency.” *Motor Vehicle Mfrs. Ass’n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Rather, the Court asks whether the agency “examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made.” *Id.* (internal quotation marks

omitted). When reviewing that explanation, the Court “must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment.” *Id.* (internal quotation marks omitted). The Court’s review is “fundamentally deferential—especially with respect to matters relating to an agency’s areas of technical expertise.” *Fox v. Clinton*, 684 F.3d 67, 75 (D.C. Cir. 2012) (cleaned up). The party challenging an agency’s action as arbitrary and capricious bears the burden of proof. *Pierce v. SEC*, 786 F.3d 1027, 1035 (D.C. Cir. 2015).

III. ANALYSIS

As explained below, the Court finds that MSN’s generic drug is consistent with FDA regulatory and statutory requirements that require a generic drug to have the same label and active ingredients as the reference drug. *See* 21 C.F.R. § 314.94(a)(8)(iv); *id.* § 314.92(a)(1); *see* 21 U.S.C. § 355(j)(2)(A)(v); *id.* § 355(j)(2)(A)(ii). The Court further finds that FDA did not act arbitrarily by excluding part of Entresto’s dosing regimen from MSN’s generic drug label. For these reasons, the Court will uphold FDA’s approval of MSN’s generic drug.

A. Labeling Sameness

The Federal Food, Drug, and Cosmetic Act requires a generic drug application to show that the “labeling proposed for the new drug is the same as the labeling approved for the [reference] drug.” 21 U.S.C. § 355(j)(2)(A)(v). The statute provides an exception for “changes required . . . because the [generic] drug and [reference] drug are produced and distributed by different manufacturers.” *Id.* That exception “permits [FDA] to approve an ANDA . . . even though the label of the generic product will not include one or more indications that appear on the label of the [reference] drug upon which the ANDA is based.” *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499 (D.C. Cir. 1996). FDA regulations further define the changes permitted under the statutory exception, to include the “*omission of an indication* or other aspect of labeling protected

by patent or accorded exclusivity.” 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). Any labeling changes must “not render the proposed [generic] drug product less safe or effective than the [reference] drug for all remaining, non-protected conditions of use.” *Id.* § 314.127(a)(7).

1. Indication Carveout

FDA’s approval of the indication carveout does not violate statutory same-labeling requirements. Under the “different manufacturer” exception, an ANDA may be “be approved for less than all of the indications for which the [reference] drug has been approved,” and the corresponding generic label may carve out excluded indications. *Bristol-Myers Squibb*, 91 F.3d 1493 at 1496, 1500. Binding Circuit law thus permits changes to generic’s label to account for patent-protected indications. The Court rejects Novartis’s argument that *Bristol-Myers Squibb* is no longer good law in the wake of *Loper Bright*, 144 S. Ct. at 2273. *See* Novartis Mem. at 22–23. In *Bristol-Myers Squibb*, the D.C. Circuit relied on its own interpretation of § 355(j)(2)(A)(v), rather than deferring to FDA’s reading under *Chevron* step two. *See Bristol-Myers Squibb*, 91 F.3d at 1499 (the question presented was “whether the Congress ha[d] directly addressed the issue . . . in dispute”).

FDA also did not contravene the statutory requirement that a generic label may not be compared to a superseded version of the reference label. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 614 (2011). Simply because the language of the generic label tracks Entresto’s original superseded label, it does not follow that that FDA “reverted back” to Entresto’s original label. *See* Novartis Mem. at 19–21. The administrative record unequivocally shows that FDA compared the generic label to “most recently approved” Entresto label. AR 2402–03 (identifying as “model labeling” as the Entresto label version approved in April 2024).

Turning to FDA’s regulations, the Court finds that the indication carveout complies with FDA regulations permitting the “*omission of an indication* or other aspect of labeling protected by patent.” 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). The Court agrees with FDA that an “omission” under the regulation must turn on the “substance of the information that is omitted—not whether that substantive omission is accomplished by adding words or deleting them.” FDA Opp’n at 21; *see* AR 2946–47 (denying Novartis’s Labeling Petition because the regulation permits approval of labeling that restricts the scope of an indication by adding words); *cf.* 21 U.S.C. § 355(j)(2)(A)(v) (the statutory provision permits “changes” to labeling, not merely deletions). The plain text of the Food, Drug, and Cosmetic Act refers to the omission of “an indication or other aspect of labeling protected by patent,” § 314.94(a)(8)(iv), not the omission of particular words from the indication statement, *see* Novartis Mem. at 22–26.⁶ Novartis’s contrary position—that a generic label may only omit patented uses by deleting words rather than adding them—puts form over substance. Under Novartis’s position, a generic drug indication statement that a “[patented drug] is approved to treat Disease (Type I, Type II, and Type III)” would permit carveouts, whereas a statement that a “[patented drug] is approved to treat all types of Disease” would not. Nothing in FDA’s regulations suggest that a shorter indication statement should result in broader patent-protections from generic carveouts, and the agency has never adopted such an approach. *See* AR 3947. FDA precedent further establishes that a substantive “omission” may be effectuated through

⁶ The Court rejects Novartis’s argument that 21 U.S.C. § 355a(o), which allows FDA to require generics that carve out pediatric indications to add warning language, implies that language additions are forbidden in other contexts. *See* Novartis Mem. at 23–24. That logic does not follow. That the statute allows FDA to require additional warning language after a pediatric indication has been omitted does not mean the statute precludes the agency from adding language to effectuate an omission. Further, Section 355a(o) states that the provision “does not affect . . . the operation of Section 355 [the generic drug provisions]” except as Section 355a(o) “expressly provide[s].” 21 U.S.C. § 355a(o)(3)(D).

the addition of words. In a matter involving the drug Velcade (bortezomib), FDA approved a carveout narrowing the drug’s indication statement through the addition of a phrase: the brand-name’s indication for the “treatment of patients with mantle cell lymphoma” was changed to “for the “treatment of patients with mantle cell lymphoma *who have received at least 1 prior therapy.*” AR 3946–47.

Here, too, MSN’s label contains a substantive omission that complies with agency regulations. While Entresto’s current label indication covers all “adult patients with chronic heart failure,” MSN’s generic label indication limits coverage to an indication that is no longer patent-protected: “adult patients with chronic heart failure *and reduced ejection fraction.*” *Compare Entresto Label § 1.1 with Generic Label § 1.1.* In substance, the carveout narrows the scope of the current Entresto indication by limiting coverage to reduced ejection fraction patients. This carveout complies with FDA regulations permitting an omission of an indication.

Finally, limiting the generic indication to reduced ejection fraction patients was not arbitrary and capricious agency action. Medical determinations about the categorization of chronic heart failure patients and the relevance of quantified ejection fraction metrics relate to FDA’s “areas of technical expertise,” to which the Court must be “fundamentally deferential.” *Fox*, 684 F.3d at 75. Novartis contends that the “medical community has transitioned away from using LVEF as a strict criterion,” and it suggests the generic indication reflects a “return to the strictly quantitative approach” disfavored by modern medicine. Novartis Mem. at 8, 26–27. But as FDA explains, it has never defined “reduced ejection fraction” by any strict numerical cutoff. Even Entresto’s original indication “did not restrict the [drug] . . . strictly to patients with LVEF less than or equal to 40 percent,” and the distinction between preserved and reduced ejection fraction patients accurately tracks clinical findings that “LVEF data below normal” reflects impaired left-

ventricle contraction. FDA Opp’n at 24–25; AR 3920–22, 3935–37. Entresto’s own label reflects that LVEF remains a relevant diagnostic criterion. *See Entresto Label* § 1.1 (“Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.”). Furthermore, even if it were supported by medical evidence, Novartis’s argument that LVEF is no longer a sound diagnostic criterion would speak to the drug’s safety and efficacy. *See* 21 C.F.R. § 314.127(a)(7). But there is no reason why limiting the drug to reduced ejection fraction patients would render the drug less “safe or effective” for those patients. *Id.* (the relevant consideration is whether the drug as safe and effective for “all *remaining*, non-protected conditions of use” (emphasis added)). If reduced ejection fraction patients could safely use the drug alongside other heart failure patients, no longer treating those other patients could not affect the drug’s medical properties for the remaining, reduced ejection fraction patients. Thus, the Court cannot say that FDA acted arbitrarily and capriciously in approving MSN’s generic indication limited to reduced ejection fraction patients.

2. *Dosing Regimen Carveout*

The Court also finds that FDA’s approval of the dosage regimen carveout was not arbitrary and capricious. In assessing FDA’s factual and policy determinations on drug safety issues, the Court cannot “substitute its judgment for that of the agency.” *State Farm*, 463 U.S. at 43. The relevant inquiry is whether the agency “examine[d] the relevant data and articulate[d] a satisfactory explanation” for its scientific conclusion, and the Court “must consider whether the [agency] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment.” *Id.* (internal quotation marks omitted). FDA’s “scientific judgment within its ‘area of expertise’” is entitled to a “high level of deference.” *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)).

The Court finds that FDA provided a reasoned scientific basis for its conclusion that carving out Section 2.6 will not render MSN’s generic drug less “safe or effective.” 21 C.F.R. § 314.127(a)(7). Section 2.6 instructs prescribers to “start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults . . . to follow the recommended dose escalation thereafter.” *Entresto Label* § 2.6. As described *supra*, Section 2.6 was based on the results of the TITRATION study. The study found that for patients not habituated to ACE inhibitors or ARBs, those who initially received 50mg of Entresto twice daily increased to 200mg over 5 weeks experienced moderately fewer side effects than those who initially received 100mg of Entresto twice daily increased to 200mg over 2 weeks.

During initial clinical review in 2015, FDA determined that TITRATION’s conservative dosing regimen “seem[ed] reasonable” because a “longer titration period with a [lower] starting dose . . . *may* reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an [ACE inhibitor] or ARB.” AR 301 (emphasis added). But the agency also found that “[a]vailable evidence does not suggest that the safety profile of [Entresto] would be significantly different between [ACE inhibitor]/ARB naïve patients and [ACE inhibitor]/ARB experienced patients.” AR 310. Importantly, FDA concluded that “the key risks of hypotension, renal impairment, hyperkalemia, and angioedema can be adequately managed through clinical monitoring and dose titration.” AR 243. Section 5 of the Entresto label—“Warnings and Precautions”—reflects that determination, and advises prescribers that the risks of hypotension, renal impairment, and hyperkalemia can be mitigated for all patients through a reduced “initial dose” of the drug. *Entresto Label* §§ 5.3–5.5.

FDA thoroughly explained its rationale for approving MSN’s generic label without the dosing regimen in a 45-page response to Novartis’s Labeling Petition. *See* AR 3910–54. The

agency applied the appropriate regulatory standard to conclude that the carveout “would not render generic sacubitril and valsartan tablets less safe or effective than [Entresto] for all remaining, nonprotected conditions of use.” AR 3948; *see University of Great Falls v. NLRB*, 278 F.3d 1335, 1340 (D.C. Cir. 2002) (an agency must apply the correct regulatory standard). The agency explained that “the results of TITRATION are not robust,” because “the small number of subjects in TITRATION limits certain interpretation of the data.” AR 3950 & n.182. Further, the agency determined that it is “unknown” “[w]hether the [S]ection 2.6 dosing modification is the ‘safest’ and ‘best-tolerated’ option” for relevant patients, because that specific regimen had only been “studied in an uncontrolled manner (i.e., [in a] single-blind run-in).” AR 3949.⁷ As a statistical matter, TITRATION “d[id] not provide a scientific basis to conclude” that a standard dosing regimen would put the relevant “patients at a greater risk of adverse reactions.” AR 3949–50. FDA’s explanation was consistent with the agency’s original 2015 findings: while Section 2.6 was “reasonable” for FDA to approve because it “may” reduce the risks of adverse reactions, the agency has never taken the position that the study’s conclusions were definitive or “necessary” for the approval of Entresto. AR 301; *see* AR 3925.

FDA also “believed at the time, and still believes, that the risk of [Entresto’s] important adverse reactions . . . can be adequately managed through labeling that describes clinical monitoring and dose titration.” AR 3950. The agency highlighted that Sections 5.3 through 5.5 of the Entresto label specifically address the risks of hypotension, renal impairment, and

⁷ “TITRATION was a supportive phase 2 trial and suggested that ACEi- or ARB-naïve/low dose patients might benefit from a slow up-titration regimen with a lower starting dose to increase tolerability and reduce the risk of adverse reactions such as hypotension, hyperkalemia, and renal impairment. Although TITRATION provided some information about the safety profiles of the standard and modified dosing regimens, for example, that more patients were able to achieve and maintain target doses of Entresto . . . the results of TITRATION are not robust.” AR 3949.

hyperkalemia, and are “sufficient for [the] purpose” of reducing those risks. AR 3951. FDA further explained that “published guidelines on [heart failure] treatment” direct “a general up-titration approach guided by tolerability,” and that prescribers’ own clinical experience further informs decisions about appropriate dosage protocols. AR 3950; *see id.* 4020 (citing guidance from the agency’s Division of Cardiology and Nephrology, explaining that “[p]rescribers are in the best position to determine an appropriate initial dose of [Entresto] using the characteristics described in [S]ection 5,” and that the “2022 [American Heart Association] Guidelines for treatment of Heart Failure support a general up-titration approach guided by tolerability”). Given other available guidance and labeling warnings, FDA concluded that Section 2.6 “is not necessary . . . information,” and that in its absence, the drug will remain “as safe and effective . . . for the remaining nonprotected conditions of use.” AR 3951.

In making this safety and efficacy determination, FDA evaluated the clinical significance of the TITRATION study, prevailing medical guidance, and prescriber best practices. *See State Farm*, 463 U.S. at 52 (holding the agency must “examine the relevant data” and “consider[] the relevant factors”). It provided a reasoned basis for its decision and concluded, in three separate instances in its thorough citizen petition response, *see* AR 3949–51, that carving out Section 2.6 would not render the drug any less “safe or effective,” *see* 21 C.F.R. § 314.127(a)(7). It cannot be said that the agency applied the wrong standard, inadequately explained its decision, or rendered “a clear error of judgment.” *State Farm*, 463 U.S. at 43.

B. Active Ingredient Sameness

Federal statute and FDA regulations provide that a generic must be “identical in active ingredient(s)” to its reference drug. 21 C.F.R. § 314.92(a)(1); *see* 21 U.S.C. § 355(j)(2)(A)(ii).

Identical active ingredients must be “the same salt . . . of the same therapeutic moiety.”⁸ 21 C.F.R. § 314.3(b) (definition of “Pharmaceutical equivalents”). Active ingredient sameness is evaluated based on the chemical structure of a drug’s finished dosage form, prior to administration. 54 Fed. Reg. at 28,881. Drug ingredients need not have the same solid state physical form to have the same chemical identity. 57 Fed. Reg. at 17,958–59. We review FDA’s scientific determinations about active ingredient sameness “only for reasonableness and consistency with the evidence in the record.” *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 678 F. Supp. 3d 20, 38 (D.D.C. 2023), *aff’d*, 108 F.4th 836 (D.C. Cir. 2024).

The Court will defer to FDA’s factual determination that Entresto and MSN’s generic contain the same two active ingredients—sacubitril sodium and valsartan disodium. *See* AR 2812–13 (Novartis Active Ingredient Petition, describing Entresto as having “two active ingredients”); AR 242 (stating that ENRESTO “is considered a fixed-dose combination drug” and identifying sacubitril and valsartan as separate components). [REDACTED]

[REDACTED]. AR 810–11.

Both labels use the same language to describe the active ingredients:

<i>Entresto Label</i> § 11 (emphasis added)	<i>Generic Label</i> § 11 (emphasis added)
ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, [and] sodium cations . . . in the molar ratio of 1:1:3[] , respectively. Following oral administration, the complex dissociates into sacubitril . . . and valsartan.	Sacubitril and valsartan tablets contain anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3 , respectively. Following oral administration, the drug substance dissociates into sacubitril . . . and valsartan.

⁸ The parties do not dispute that both drugs share the same two active moieties. *See* FDA Opp’n at 30; Novartis Reply at 14.

In the Entresto product, prior to administration, the ingredients take the form of a co-crystal—a contiguous lattice complex in which the two chemically distinct compounds are linked by non-ionic bonds. AR 2819–20; *see* FDA Opp’n at 38. The parties dispute whether MSN’s generic product takes the form of a “co-crystal,” *see* FDA Opp’n at 38–39, or whether it is a physical mixture of “two independent salts,” *see* Novartis Mem. at 38–39. But as FDA explains, this distinction is irrelevant to the sameness inquiry: a “a co-crystal composed of two active ingredients” is merely a different solid state form of the ingredients, “not a new active ingredient.” FDA Opp’n at 39 (citing *Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals* at 3 & n.8); *see* FDA, *Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism* at 5-6 (July 2007) (“[D]ifferences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals.”).

Novartis argues that because the terms “sacubitril” and “valsartan” are used in Entresto’s approved drug application and the Orange Book, FDA’s pivot to the more specific scientific nomenclature—“sacubitril sodium” and “valsartan disodium”—reflects an agency flip-flop. *See* Novartis Reply at 13. While the technical usages of the standalone rather than the “(di)sodium” terms can reflect a difference in chemical identity, that is not the case here. As explained *supra*, “sacubitril” and “valsartan” refer in the technical sense to the protonated acids, not the anionic forms, of those compounds. But that nomenclature distinction cannot be dispositive because the protonated acids “sacubitril” and “valsartan” are not found in Entresto—by Novartis’s own characterization, Entresto has always been labeled as containing the *anionic* compounds. The nomenclature distinction thus does not reflect any difference in the chemical identity of the active drug ingredients.

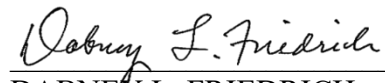
FDA determined that Entresto is not a “different salt” from MSN’s generic sacubitril sodium/valsartan disodium, as Novartis argues. *See* Novartis Mem. at 5–6. (citing 54 Fed. Reg. at 28,881); AR 58 (noting that “structural X-ray diffraction” and “spectroscopic characterization” show the Entresto complex is a co-crystal rather than a salt). FDA explained that Entresto is at most a different solid state physical form of the same salts, and the agency has consistently treated it as such. *See* AR810–11 ([REDACTED]

[REDACTED]). As described in the denial of Novartis’s Active Ingredient Petition, under longstanding agency guidance, “different physical forms do not prevent a demonstration of active ingredient sameness.” AR 2896; *see* AR 2819–20.

FDA’s determination on chemical identity sameness reflects its reasoned “scientific analysis,” which deserves “a high level of deference.” *Pharm. Mfg. Rsch. Servs., Inc. v. FDA*, 957 F.3d 254, 265 (D.C. Cir. 2020) (quotation marks omitted). It is pure scientific judgment that Entresto and MSN’s generic contain the same compounds with the same chemical identities. “A court is ill-equipped to second-guess that kind of agency scientific judgment under the guise of the APA’s arbitrary and capricious standard.” *Cytosol Therapeutics, Inc. v. FDA*, 715 F.3d 922, 927 (D.C. Cir. 2013). Instead, a court’s review is limited to whether the “FDA’s assessment [is] both reasonable and reasonably explained.” *Id.* Because FDA’s determination that Entresto and MSN’s generic contain the same active ingredients was rational, carefully explained, and consistent with the record evidence, the Court will not “unduly second-guess[]” its “scientific judgment[.]” *Pharm. Mfg. Rsch. Servs.*, 957 F.3d at 262 (quotation marks omitted).

CONCLUSION

For these reasons, the Court finds that FDA's actions did not violate the APA, the Federal Food, Drug, and Cosmetic Act, or the agency's implementing regulations. The Court denies the plaintiff's motion for summary judgment and grants the federal and the intervenor-defendants' cross motions for summary judgment. A separate order consistent with this decision accompanies this memorandum opinion.


DABNEY L. FRIEDRICH
United States District Judge

October 13, 2024