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May 28, 2024

Re: Docket No. FDA-2019-P-1893

Dear Dr. Kayath:

This letter responds to the citizen petition you submitted on behalf of Novartis Pharmaceuticals Corporation (Novartis or Petitioner) and received by the Food and Drug Administration (FDA or Agency) on April 18, 2019 (Petition). In the Petition, Novartis asks FDA to take the following actions:

(1) Require [abbreviated new drug applications] ANDAs that reference [the reference listed drug (RLD) Entresto (sacubitril and valsartan) tablets] to demonstrate [active ingredient] sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form, i.e., sacubitril and valsartan in ionic coordination with sodium with 1:1:3 stoichiometry;

(2) Revise FDA's [draft product-specific guidance on sacubitril and valsartan oral tablets (Draft Sacubitril/Valsartan PSG or Draft PSG)] to recommend that [active ingredient] sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic[1] is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; and

(3) Further revise the [Draft Sacubitril/Valsartan PSG] to include:

a. [T]he primary active metabolite, sacubitrilat, as an additional analyte for purposes of establishing [bioequivalence] BE;

b. [M]easurements to assess the [pharmacokinetics] of each analyte relative to one another to ensure comparability between test product and the RLD product; and

c. [A]n additional in vivo study to establish bioequivalence between the RLD 24 mg [milligram]/26 mg strength tablet, and the generic counterpart at the same dose strength.[2]

[1] The term *generic* is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act (21 U.S.C. 355(j)).

[2] Petition at 3-4.

FDA has carefully considered the information submitted in Novartis's Petition and appended exhibits, as well as other relevant information identified by FDA. The Petition is denied in all respects for the reasons stated below.[3]

I. BACKGROUND

A. Entresto (Sacubitril and Valsartan) Tablets

Entresto (sacubitril and valsartan) tablets (new drug application (NDA) 207620) were first approved on July 7, 2015 (hereafter, Entresto). Novartis is the current application holder for Entresto. Entresto is a fixed-combination of sacubitril and valsartan available in the following strengths: 24 mg/26 mg, 49 mg/51 mg, and 97mg/103 mg. Valsartan is an angiotensin II receptor blocker and a previously approved drug that is widely marketed for hypertension and heart failure. Valsartan does not undergo significant metabolism.[4] Sacubitril is a neprilysin inhibitor that received 5 years of new chemical entity exclusivity, which, with the addition of pediatric exclusivity, expired on January 7, 2021. Sacubitril is a prodrug that undergoes metabolism to form the active metabolite sacubitrilat (referred to by Novartis as "LBQ657"), which inhibits neprilysin and is not further metabolized.[5] Entresto is currently approved for adult and pediatric heart failure indications.[6]

The active ingredients in Entresto are sacubitril sodium and valsartan disodium, which are arranged in the physical form of a co-crystal, existing as a hemipentahydrate and also characterized, in this case, as a type of complex (referred to by Novartis as "LCZ696").[7] Entresto's labeling describes the drug as follows: "[Entresto] contains a complex comprised of

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[3] Today, FDA approved the following ANDAs for sacubitril and valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg: ANDA 213605, ANDA 213682, and ANDA 213676.

[4] See Petition at 3-4.

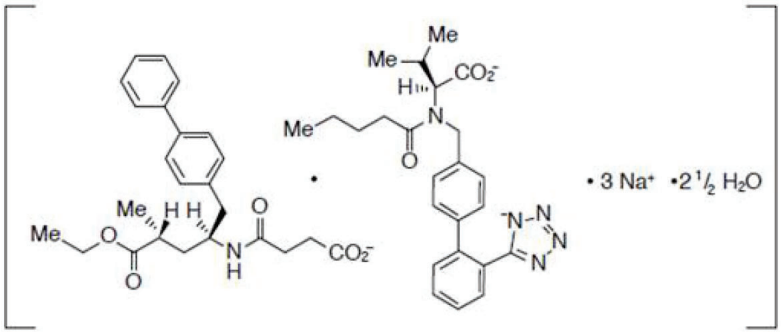
[5] Petition at 6.

[6] See Entresto Prescribing Information, Indications and Usage (Apr. 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/207620s025,218591s000lbl.pdf("**1.1 Adult Heart Failure** – [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 [see *Clinical Studies (14.1)*] **1.2 Pediatric Heart Failure** – [Entresto] is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. [Entresto] reduces NT-proBNP and is expected to improve cardiovascular outcomes.").

[7] See NDA 207620, Office Director Memo at 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ODMemo.pdf, stating that:

> LCZ696 is a co-crystal, a type of sodium salt complex . . . In an addendum to the Quality review, [the office of Pharmaceutical Quality (OPQ)] noted that both descriptions correctly represent the chemical nature of the active ingredient [sic] and are scientifically valid. The structural X-ray diffraction data submitted demonstrate that the active ingredient [sic] meets the criteria delineated in FDA Guidance Regulatory Classification of Pharmaceutical Co-Crystals (April 2013) for a co-crystal, based on orthogonal spectroscopic characterization data, evidence of dissociation in vivo, and the non-ionic interactions between the individual components. The active ingredient [sic] can also be considered a complex, however, based on the IUPAC Gold Book definition: a molecular entity formed by loose association involving two or more molecular entities (ionic or neutral); bonding is normally non-covalent.

anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively."[8] The labeling also provides the empirical formula of the Entresto complex or co-crystal ($C_{48}H_{44}N_6O_8Na_3$ 2.5 H_2O) and the following chemical structure of the active ingredients:[9]



The chemical structure depicted in the Entresto labeling shows a sacubitril anion (which has one pKa) with one negative charge and a valsartan anion (which has two pKas) with two negative charges as well as the three positively charged sodium (Na+) cations that interact with the anions to provide for the active ingredients, sacubitril sodium and valsartan disodium, respectively, comprising Entresto.[10] The chemical structure also depicts the water molecules (H_2O) that make the complex a hemipentahydrate. Those components are present in the finished dosage form of Entresto in a 1:1:3:2.5 molar ratio, respectively, and are not ionically bound.[11] The Entresto co-crystal dissociates rapidly in vivo to sacubitril and valsartan,[12] and as such, there is no systemic

[8] See Entresto Prescribing Information, 11 Description (Apr. 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/207620s025,218591s000lbl.pdf.

[9] FDA notes that a given chemical compound may be described by a series of symbols that represent the actual number and kind of atoms, i.e., the molecular formula. The particular spatial arrangement of this specified number and kind of atoms is called the structural formula. The term *chemical structure* is commonly used to encompass both molecular and structural information, i.e., the chemical structure of a given compound may be described as a series of symbols that represent the number, kind, and spatial arrangement of atoms, according to certain conventions. Chemical compounds may exist in many physical forms. Examples of different physical forms include different phases (solid, liquid, and gas) and different polymorphs. Although different forms may have very different appearances and physical characteristics, they consist of the same primary chemical structure.

[10] Under the Agency's long-standing practice, FDA generally considers an active ingredient to be the entire molecule, or ion, including the portions of the molecule that cause the drug to be a salt or ester. See, e.g., the definition of *pharmaceutical equivalent* in 21 CFR 314.3(b) (". . . identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety"). Consistent with the Agency's salt nomenclature policy, however, "the applicant was advised to label the drug product strengths based on the fixed dose combination with the free acid/base of both drug substances as the basis for strength expression" (NDA 207620, Clinical Review at 23). See also FDA's guidance for industry *Naming of Drug Products Containing Salt Drug Substances* (June 2015). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] See NDA 207620, Office Director Memo at 2.

[12] See, e.g., NDA 207620, Clinical Pharmacology and Biopharmaceutics Review(s) at 19, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ClinPharmR.pdf; see also NDA 207620, Medical Review(s) at 13 ("Following oral administration, LCZ696 dissociates into valsartan and the

exposure to the co-crystal. Entresto has been consistently viewed as a fixed-combination product from a regulatory perspective.[13]

B. Applicable Statutory and Regulatory Background

1. ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to, among other things, add section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to submit evidence to establish the safety and effectiveness of the proposed generic drug product.[14] Instead, an ANDA applicant relies on the Agency's previous finding that the RLD[15] is safe and effective. To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).[16] In addition, an ANDA must contain sufficient information to show that the generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

2. Active Ingredient Sameness

Section 505(j)(2)(A)(ii)(II) of the FD&C Act states that, for a listed drug with more than one active ingredient, an ANDA must contain information to show that the active ingredients of the

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prodrug sacubitril . . . in a 1:1 molar ratio."), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000MedR.pdf.

[13] See, e.g., NDA 207620, Office Director Memo at 3, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ODMemo.pdf; see also NDA 207620, Medical Review(s) at 11 ("LCZ696 is considered a fixed-dose combination drug; therefore, according to the Agency's regulations for such products outlined in 21 CFR 300.50, each component must contribute to the effect."); Petition at 8 ("[Entresto] was reviewed and approved as a combination of sacubitril and valsartan . . . .").

[14] See, generally, section 505(j)(2)(A) of the FD&C Act.

[15] An *RLD* is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3). A *listed drug* is a new drug product that has been approved under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the FD&C Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness (Ibid.). RLDs are identified in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

[16] See section I.B.3. for a discussion of "bioequivalence."

generic drug product are the "same" as those of the listed drug. FDA regulations in 21 CFR 314.3(b) provide that:

> *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. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Under section 505(j)(4)(C)(ii) of the FD&C Act, we must approve an ANDA referencing a listed drug that has more than one active ingredient unless, among other things, the ANDA contains insufficient information to show that the active ingredients are the same as those of the listed drug.

These statutory provisions do not describe the type or amount of information that an ANDA applicant must submit to demonstrate that the active ingredients in the generic drug product are the same as the active ingredients in the RLD, nor do these provisions describe the type or amount of information on which we may rely in determining whether the ANDA applicant has provided sufficient information to show that the active ingredients are the same.

Parallel FDA regulations implementing these statutory provisions (i.e., section 505(j)(2)(A)(ii)(II) and (j)(4)(C)(ii)) can be found in 21 CFR 314.94(a)(5)(ii) and 314.127(a)(3)(ii), respectively. FDA regulations also provide that an ANDA is suitable for consideration and approval if the generic drug product is the same as the RLD (21 CFR 314.92(a)(1)). Specifically, § 314.92(a)(1) states that the term "same as" means, among other things, "identical in active ingredient(s)." In the preamble to the 1992 final rule implementing title I of the Hatch-Waxman Amendments, we specifically rejected the suggestion that we adopt a requirement that active ingredients "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process, and that the stereochemistry characteristics and solid state forms of the drug have not been altered."[17] Instead, we adopted a more flexible approach, stating that we would "consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity."[18]

As FDA's regulations and preamble reflect, and as the courts have repeatedly acknowledged,[19] we have broad discretion in determining whether an ANDA applicant has submitted sufficient

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[17] See the final rule "Abbreviated New Drug Application Regulations" (57 FR 17950 at 17958–17959, April 28, 1992).

[18] Ibid. at 17959.

[19] See, e.g., *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998) (*Serono*). In *Serono*, the United States Court of Appeals for the District of Columbia Circuit upheld as reasonable the Agency's interpretation of the "sameness" statutory requirement, as well as the Agency's interpretation of the word "identical" in § 314.92(a)(1) (158 F.3d at 1321). The court noted that the statute says nothing at all about the type of information an applicant must submit to demonstrate "sameness" or about the type of information upon which FDA may rely (*Serono* at 1319). The court characterized the sameness provision as a "broad grant of discretion" to the Agency with respect

information upon which the Agency can reasonably conclude that the generic drug product's active ingredients are the "same" as those of the RLD.

3. Bioequivalence

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.[20] Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . ..[21]

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and to an extent that is not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an effect on the rate and extent to which the active ingredient becomes available at the site of action.

As discussed further below, the statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include in vivo data (data from a study on human subjects), in vitro data (data from laboratory studies), or a combination of in vivo and in vitro data.[22] This flexibility is reflected in FDA's regulations, which describe the types of evidence that may be used to establish bioequivalence:

> FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products . . .. The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring

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to the information it may consider and noted that the phrase "must be read in the context of the kind of drug at issue" (Ibid.).

[20] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"), 21 CFR 314.94(a)(7) (requiring that an ANDA contain information to show that the drug product is bioequivalent to the RLD), and 21 CFR 314.127(a)(6)(i) (stating that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

[21] See also 21 CFR 314.3(b) and 21 CFR 320.23(b).

[22] See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with discretion to determine whether in vitro or in vivo bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process.").

> bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[23]

Section 320.24(b) (21 CFR 320.24(b)) of FDA's regulations describes acceptable BE methods in general descending order of accuracy, sensitivity, and reproducibility. The BE methods include: (1) in vivo pharmacokinetic (PK) studies of the active ingredient or, when appropriate, its active metabolites in whole blood, plasma, serum, or other appropriate biological fluid or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolite(s) are measured as a function of time; (3) in vivo studies measuring acute pharmacodynamic effect; (4) comparative clinical endpoint studies; and (5) other in vitro studies acceptable to FDA (usually a dissolution rate test) that ensure human in vivo bioavailability.[24] In addition, consistent with section 505(j)(8)(C) of the FD&C Act, § 320.24(b)(6) of the regulations states that FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." The Agency's authority to make BE determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards for approval;[25] (2) permitting the Agency to use the latest scientific advances in approving drug products;[26] (3) protecting the public by ensuring only safe and effective generic drugs are approved for marketing;[27] and (4) making more safe and generic drugs available.[28]

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[23] § 320.24(a). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it would determine the appropriate bioequivalence methodology on a case-by-case basis: "Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . *is determined on a case-by-case basis*, depending on the drug under study." See the final rule "Abbreviated New Drug Application Regulations" (57 FR 17950 at 17972, April 28, 1992) (emphasis added).

[24] See § 320.24(b).

[25] See 21 CFR 320.25(a) (stating that a "guiding principle" for the conduct of an in vivo bioavailability study is "that no unnecessary human research should be done") and the proposed rule "Abbreviated New Drug Application Regulations" (54 FR 28872 at 28883, July 10, 1989) (in discussing 21 CFR 320.22, stating that "[t]he agency does not believe that Congress intended that unnecessary human research be conducted . . . . [I]f the agency concludes that bioequivalence can be demonstrated by in vitro tests, the agency proposes to require only such tests rather than in vivo studies.").

[26] See "Part 320—Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement" (42 FR 1624 at 1629, January 7, 1977). ("As with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement.")

[27] See *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992) (noting that one underlying policy of the Hatch-Waxman Amendments is to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

[28] Ibid. (finding that the purposes of the Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866–867 (D.D.C. 1994) (finding that the BE waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act," including making safe and affordable generic drugs available).

For most systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood, after administration of a single dose or multiple doses of each drug product to healthy volunteers.[29] For systemically acting drug products with active metabolites, we generally recommend that ANDA applicants demonstrate bioequivalence based on a comparison of parent drug concentrations in an accessible biologic fluid, unless accurate assay quantitation is not possible using state-of-the-art-technology.[30] We generally recommend that ANDA applicants measure only the parent drug, rather than metabolites, because the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.[31] We generally recommend that ANDA applicants analyze the parent drug measured in these bioequivalence studies using a confidence interval approach.[32]

Standard bioequivalence PK studies are conducted using a two-treatment crossover study design, randomly separating a limited number of subjects into test and reference drug groups. Single doses of the test and reference drugs are administered, and blood, serum or plasma concentrations of the drug are measured over time. The rate and extent of absorption are statistically evaluated. The relevant PK parameters calculated from these data include the area under the concentration versus time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant PK parameter is the maximum or "peak" drug concentration (C_{max}). C_{max} is used to reflect the rate of absorption.

For in vivo PK tests, FDA generally considers two products to be bioequivalent when the 90-percent confidence interval for the log-transformed ratio of geometric means for the PK parameters AUC and C_{max} are entirely within an 80.00- to 125.00-percent acceptance interval.[33]

Although in vivo PK studies are often the preferred method of demonstrating bioequivalence, they are not required (or even preferred) in every instance. When an NDA contains several strengths and an ANDA applicant demonstrates that one strength is bioequivalent, FDA

[29] See section 505(j)(8)(B) of the FD&C Act; see also FDA's draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Aug. 2021) (Draft ANDA BE Guidance). When final, this guidance will represent FDA's current thinking on this topic.

[30] Draft ANDA BE Guidance at 15.

[31] See, e.g., Citizen Petition Denial Response from FDA's Center for Drug Evaluation and Research (CDER) to Amedra Pharmaceuticals LLC (FDA-2013-P-0766) at 6 (noting that FDA generally recommends that ANDA applicants demonstrate bioequivalence based on a comparison of parent drug concentrations in an accessible biologic fluid because the concentration-time profile of the parent drug is a better indicator of differences in formulation and manufacturing between a proposed generic drug and the RLD).

[32] In analyzing in vivo BE studies, FDA generally uses a 90-percent confidence interval.

[33] See FDA's draft guidance for industry *Statistical Approaches to Establishing Bioequivalence* (Dec. 2022).

regulations provide for a waiver of an in vivo showing of bioequivalence for the other strengths under certain circumstances. For example, the regulation at § 320.22(d)(2) generally provides that FDA shall waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of certain immediate-release drug products described in an ANDA if:

> The [test product for which a waiver is sought] is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another [strength] for which the same manufacturer has obtained approval; and. . . (i) [t]he bioavailability of this other [strength] has been measured; (ii) [b]oth [strengths] meet an appropriate in vitro test approved by FDA; and (iii) [t]he applicant submits evidence showing that both [strengths] are proportionally similar in their active and inactive ingredients.[34]

These provisions presume that the applicable strengths of the RLDhave resulted in dose proportional exposure in vivo[35] (or have otherwise demonstrated a relationship between the bioavailability of the different strengths that suggests that a waiver is appropriate). Thus, FDA will waive in vivo bioequivalence for lower strengths of immediate-release drugs if the RLD shows dose proportional exposure in vivo and if the other requirements in the regulations are met. This is the case even when the RLD does not show compositional proportionality of active and inactive ingredients. In the absence of dose proportional exposure for the strength of the RLD (or some other reason for waiver), however, each strength of an ANDA product would need to be demonstrated to be bioequivalent to the corresponding strength of the product it references.

The choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug, and Congress assigned this decision to FDA. Congress intended to grant FDA wide discretion to establish bioequivalence standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments, and courts have recognized FDA's discretion to determine how the bioequivalence requirement should be met for a product or class of products, as long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[36]

C. Draft Product-Specific Guidance on Sacubitril; Valsartan

FDA's June 2010 guidance for industry *Bioequivalence Recommendations for Specific Products* describes the Agency's process for making available to the public FDA's guidance on the design

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[34] See 21 CFR 320.22(d).

[35] *Dose proportional exposure* and *dose proportional exposure in vivo*, as used interchangeably throughout this response, can be demonstrated by showing that the in vivo PK exposure parameters of AUC and C_{max} increase in direct proportion to the increase in strengths or doses of the drug.

[36] See, e.g., *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 865 (D.D.C. 1994) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot*, 955 F.2d 1103, 1106 (D.C. Cir. 1993)); see also *Fisons,* 860 F. Supp. at 866-867 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Schering Corp.*, 51 F.3d at 397-400 (3d Cir. 1995).

of bioequivalence studies for specific drug products.[37] Currently, FDA periodically publishes notices in the *Federal Register* announcing the availability of draft, revised draft, and final versions of product-specific guidances (PSGs). These documents are available on FDA's website.[38]

FDA considers comments received on PSGs when developing its final guidances. As with Agency guidance in general, these PSGs describe the Agency's current thinking and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Applicants following our PSGs have an expectation that FDA will agree that their approach to establishing bioequivalence is appropriate. However, applicants may confer with the Agency on using a different approach for establishing bioequivalence. Recommendations made in a draft or final guidance do not bind the Agency or the public. Further, even in the absence of a PSG, FDA has the authority to approve a product supported by bioequivalence data that meet the applicable statutory and regulatory requirements.

In a *Federal Register* notice dated April 15, 2016 (81 FR 22283), we announced the availability of the Draft Sacubitril/Valsartan PSG).[39] The Draft Sacubitril/Valsartan PSG recommends the following two studies:

- A single-dose, two-way crossover in vivo bioequivalence study with PK endpoints obtained from healthy males and females[40] in the general population, under fasting conditions, using sacubitril/valsartan tablets with a product strength of 97 mg/103 mg, administered orally.

- A single-dose, two-way crossover in vivo bioequivalence study with PK endpoints obtained from healthy males and females[41] in the general population, under fed conditions, using sacubitril/valsartan tablets with a product strength of 97 mg/103 mg, administered orally.

[37] This guidance states that the Agency intends to develop bioequivalence recommendations based on its understanding of the characteristics of the listed drug, information derived from published literature, and Agency research and consultations within different offices in FDA's CDER as needed based on the novelty or complexity of the bioequivalence considerations. Specific product recommendations may contain differing amounts of detail and background information depending on the product and will be revised as appropriate to ensure that the most up-to-date bioequivalence information is available to the public (Ibid. at 2-3).

[38] The Product Specific Guidances for Generic Drug Development web page is available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

[39] The Draft Sacubitril/Valsartan PSG is available on FDA's website at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development. As stated in the Draft PSG, the guidance, once finalized, will represent the FDA's current thinking on this topic.

[40] The Draft PSG notes that "[f]emale subjects should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study."

[41] The Draft PSG notes that "[f]emale subjects should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study."

For each study, both sacubitril and valsartan are quantified in the plasma to evaluate bioequivalence based on the 90-percent confidence interval.[42] The Draft Sacubitril/Valsartan PSG further recommends that generic applicants may request a waiver of in vivo testing of the 24 mg/26 mg and 49 mg/51 mg strengths, "based on (i) acceptable [bioequivalence] studies on the 97 mg/103 mg strength, (ii) comparable dissolution testing on all strengths, and (iii) proportional similarity in the formulations of all strengths."[43]

The recommendations in the Draft PSG reflect certain scientific determinations FDA is sharing with potential applicants that develop generic sacubitril/valsartan drug products referencing Entresto as the RLD. As noted in the Petition, Novartis has submitted a comment to the public docket for the Draft PSG.[44] As discussed further below, the Draft PSG is consistent with the Agency's current recommendations for demonstrating bioequivalence of sacubitril/valsartan tablets.

D. Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals

In a *Federal Register* notice dated February 15, 2018 (83 FR 6863), we announced the availability of our guidance for industry *Regulatory Classification of Pharmaceutical Co-Crystals* (Rev. 1, February 2018) (Co-Crystal Guidance). The Co-Crystal Guidance provides applicants planning to submit NDAs and ANDAs with information on the appropriate regulatory classification of pharmaceutical co-crystal solid-state forms. The Co-Crystal Guidance also provides information about the data that applicants should submit to support the appropriate classification of a co-crystal as well as the regulatory implications of the classification. The Co-Crystal Guidance provides a definition of "co-crystals" and highlights some of their advantages:

> Co-crystals are crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ('coformers'), in the same crystal lattice. Pharmaceutical co-crystals have provided opportunities for engineering solid-state forms beyond conventional solid-state forms of an API, such as salts and polymorphs. Co-crystals can be tailored to enhance drug product bioavailability and stability and to enhance the processability of APIs during drug product manufacture.

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[42] Draft PSG at 1.

[43] Ibid.

[44] Petition at 3 (citing Novartis Comments, Docket. No. FDA-2007-D-0369-0437, https://www.regulations.gov/document?D=FDA-2007-D-0369-0437). The present discussion is limited to the issues raised in this Petition and does not constitute a full review or finalization of the Draft Sacubitril/Valsartan PSG. Novartis should submit any additional comments about the recommendations in the draft guidance to the draft guidance docket (Docket No. FDA-2007-D-0369). FDA will review and consider all significant comments received in the context of any future revisions or finalization of the Draft PSG. In addition, as noted above, whether or not Agency has finalized the Draft PSG, if the Agency determines that, as required by the statute and regulations (21 U.S.C. 355(j)(2); 21 CFR 314.94), an ANDA contains sufficient evidence that the proposed generic drug product is bioequivalent to its RLD and the application meets the other requirements for approval, FDA will approve the ANDA.

> Another advantage of co-crystals is that they generate a diverse array of solid-state forms for APIs that lack ionizable functional groups, which is a prerequisite for salt formation.[45]

The Co-Crystal Guidance explains that "[c]o-crystals are distinguished from salts because unlike salts, the components that co-exist in the co-crystal lattice with a defined stoichiometry interact nonionically."[46] The Co-Crystal Guidance further explains that an active ingredient with a pharmaceutically acceptable coformer that meets the scientific conditions discussed in the guidance can be considered to be a pharmaceutical co-crystal and has a regulatory classification similar to that of a polymorph of the active ingredient.[47] The Co-Crystal Guidance further explains that such a pharmaceutical co-crystal is not regarded as a new active ingredient.[48] Specifically, the Co-Crystal Guidance explains that "[f]rom a regulatory perspective, drug products that are designed to contain a new co-crystal are considered analogous to a new polymorph of the API" and that "[a] co-crystal that is composed of two or more APIs (with or without additional inactive coformers) will be treated as a fixed-dose combination product and not a new single API."[49]

II. SUMMARY OF PETITIONER'S ARGUMENTS

Novartis contends that FDA should (1) "refrain from approving an ANDA that fails to establish [active ingredient] sameness based on sacubitril, valsartan and sodium, in ionic complex, in a 1:1:3 stoichiometry" and revise the Draft Sacubitril/Valsartan PSG to recommend such sameness criteria;[50] and (2) further revise the Draft PSG to include (a) the active metabolite, sacubitrilat, as an additional analyte to measure for purposes of establishing bioequivalence, (b) measurements to assess the pharmacokinetics of each analyte relative to one another to ensure comparability between test product and Entresto, and (c) an additional in vivo study to establish bioequivalence to the 24 mg/26 mg strength of Entresto.[51]

A. Request That ANDA Applicants Match the "Coordinated Ionic Structure" of the Active Ingredients in Entresto and That FDA Revise the Draft Sacubitril/Valsartan PSG To Include Such Standard for Active Ingredient(s) Sameness

Novartis asserts that "[t]he chemical identity of the active ingredients in [Entresto] is defined by specific ionic interactions comprising a specific chemical structure."[52] Therefore, according to Novartis, "each active ingredient in the finished dosage form of a proposed generic to [Entresto]

[45] Co-Crystal Guidance at 1-2.

[46] Ibid. at 2.

[47] Ibid. at 3.

[48] Ibid.

[49] Ibid.

[50] See, e.g., Petition at 19-20.

[51] See, e.g., Petition at 21-25.

[52] Petition at 14.

must be identified and shown to exhibit the same chemical structure—the same coordinated ionic structure as the RLD—to conform to fundamental standards of [active ingredient] sameness."[53] More specifically, Novartis describes the basis of its contention as follows:

> [Entresto] was reviewed and approved as a combination of sacubitril and valsartan, but it does not contain a physical mixture of these components. It contains a complex of sacubitril and valsartan in their anionic forms, and sodium cations, along with water molecules, in the molar ratio of 1:1:3:2.5, respectively. The 1:1:3 sacubitril:valsartan:sodium complex is a stable, well-defined chemical structure, with defined stoichiometry. This complex structure defines the chemical structure of sacubitril and valsartan as they co-exist in the finished drug product prior to administration, and as such, must serve as the basis of [active ingredient] sameness under FDA's established framework.[54]

According to Novartis, "in some cases," the active ingredient of a drug product includes "the specific complex present in the drug product."[55] Novartis claims that LCZ696's "chemical arrangements are so efficient that all carbonyl and carboxy oxygen atoms of valsartan and sacubitril are associated with multiple sodium ions."[56] According to Novartis, "[t]he sodium ions are therefore not uniquely associated to distinct anions of either sacubitril or valsartan, which would be the case for a physical mixture of the individual sodium salts of sacubitril and valsartan."[57] Novartis claims that certain X-ray crystallography data depicts the structure of LCZ696 in Figure 1 of the Petition.[58]

Furthermore, Novartis asserts that it conducted various X-ray powder diffraction (XRPD) spectroscopy, solid state nuclear magnetic resonance (NMR) spectroscopy, and attenuated total reflectance-Fourier-transform infrared spectroscopy (ATR-FTIR) studies, in order to further "elucidate the chemical structure" of LCZ696 in Entresto.[59] Novartis reports results of those studies in Figures 2, 3a, 3b, and 4.[60] Novartis contends that the results of the XRPD, NMR, and ATR-FTIR studies "show that LCZ696 is distinct from a physical mixture of the individual sodium salts of sacubitril and valsartan" (i.e., sacubitril sodium and valsartan disodium).[61]

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[53] Ibid.

[54] Petition at 8.

[55] Petition at 7 (footnote omitted).

[56] Petition at 8.

[57] Petition at 9.

[58] Petition at 9-10 (citing L Feng et al., 2012, LCZ696: A Dual Acting Supramolecular Complex, Tetrahedron Letters, 53(3):275-276).

[59] Petition at 10.

[60] Petition at 9-12. Specifically, Figure 1 claims to show the X-ray single crystal structure of the LCZ696; Figure 2 claims to show the XRPD spectroscopy of LCZ696 versus individual components of LCZ696; Figures 3a and 3b claim to provide a comparison of the solid state 13C-NMR spectra of LCZ696 versus a 1:1 physical mixture of sacubitril sodium and valsartan disodium; and Figure 4 claims to show the ATR-FTIR spectra of LCZ696, sacubitril sodium, and valsartan disodium.

[61] Petition at 10 and 12.

Novartis asserts that FDA previously "observed that the validation data in the [Entresto] NDA was deficient in that the identity test did not distinguish LCZ696 from a 1:1 mixture of sacubitril and valsartan."[62] Novartis further asserts that it "informed FDA of the development of two additional identity tests, an FTIR and X-ray crystallography test, both of which have been validated to distinguish LCZ696 from the individual components, sacubitril and valsartan."[63] According to Novartis, its response to FDA "confirmed . . . that the drug substances in the finished dosage form of the product exist as a specific complex."[64]

Novartis asserts that "[s]acubitril and valsartan are not isolated and controlled in the manufacture of the finished drug product" and that drug substance controls "are imposed primarily at the level of the LCZ696 complex, as agreed to by FDA."[65] Novartis contends that "[w]hile FDA used the co-crystal guidance to describe LCZ696 and facilitate the [chemistry, manufacturing, and controls] CMC discussions, the term 'co-crystal' was used informally, with the agency acknowledging that LCZ696 is more like 'a drug substance salt form.'"[66] Novartis acknowledges that "FDA . . . clarified that a co-crystal composed of units of two or more [active ingredients], with or without additional inactive co-formers, would be treated as a fixed-dose combination and not a new single [active ingredient]."[67] Contrasting the Co-Crystal Guidance's definitions of "co-crystals" and "salts," Novartis asserts that "co-crystals are governed and defined by non-ionic interaction."[68] Novartis further asserts that "the chemical structure of sacubitril and valsartan in the finished dosage form [of Entresto] are [sic] defined by their ionic interactions with sodium ions resulting in the above-described complex structure."[69] Thus, according Novartis, "under FDA's definition, LCZ696 is not a co-crystal, but nonetheless remains a combination of drug substances."[70]

Novartis asserts that "[t]he distinct chemical structure of the active ingredients in [Entresto] is reflected in physico-chemical properties that are distinctly different from those that would exist in a physical mixture of sacubitril and valsartan, or a mixture of sacubitril and valsartan salts . . . ."[71] Novartis contends that the "LCZ696 exhibits faster dissolution rate and more favorable dissolution profile than the physical mixture of valsartan and sacubitril calcium in all conditions" tested by Novartis.[72] Novartis further contends that sacubitril and valsartan in Entresto have "specific solubility profiles," and that valsartan showed "higher solubility when delivered from LCZ696

[62] Petition at 12 (citing "NDA 207620, Mid-Cycle Information Request, February 19, 2015").

[63] Petition at 12 (citing Novartis Response to Mid-Cycle Information Request (March 11, 2015)).

[64] Petition at 12.

[65] Ibid.

[66] Petition at 13 (citing Type B Pre-NDA Meeting, Minutes, (July 14, 2014)).

[67] See Petition at 14. This is consistent with the Co-Crystal Guidance at 3.

[68] Petition at 13-14.

[69] Petition at 14.

[70] Ibid.

[71] Petition at 14-15.

[72] Petition at 15-16 (citing Figures 5-7).

compared to the solubility for valsartan when delivered as valsartan free acid."[73] Novartis asserts that "the distinct chemical structure of sacubitril and valsartan in LCZ696 is evidenced [in situ]," contending that "to achieve similar valsartan exposures in humans, ~60% more valsartan administered as a physical mixture is required than that administered as LCZ696."[74] Novartis contends that such physicochemical properties (i.e., dissolution rate, solubility, and valsartan exposure) "provide further confirmation that the active ingredients in [Entresto] have a defined relationship at the level of chemical structure."[75]

Novartis contends that any ANDA formulation of Entresto based on (1) "a physical mixture of individual sodium salts (or other salts) of sacubitril and valsartan," (2) "sacubitril and valsartan as free acids," or (3) sacubitril and valsartan "in an anionic state in association with a metal or cation other than Na^+" "would violate principles of ANDA sameness" and should not be approved for marketing.[76] According to Novartis, "one complex with coordinated ionic bonds between anionic sacubitril, anionic valsartan, and cationic sodium (Na^+) ions in a defined 1:1:3 (sacubitril:valsartan:sodium) stoichiometry"[77] is the chemical structure that "establishes the identity of each of the active ingredients in [Entresto] that a proposed generic drug sponsor must match."[78] To that end, Novartis specifically contends that "FDA must refrain from approving an ANDA that fails to establish [active ingredient] sameness based on sacubitril, valsartan and sodium, in ionic complex, in a 1:1:3 stoichiometry."[79]

Novartis further asserts that "the chemical identity of the active ingredients [in Entresto] is complex and novel," and therefore FDA:

> . . . should revise the [Draft Sacubitril/Valsartan PSG] to include recommendations for generic drug applicants to establish that the proposed product comprises a complex with the same 1:1:3 sacubitril:valsartan:sodium stoichiometry that defines the chemical structure of the sacubitril and valsartan active ingredients in the finished drug product.[80]

Novartis states that it submitted the Petition in part "to formally request . . . that FDA revise the Draft Guidance to include [active ingredient] sameness criteria" because it contends that "[active ingredient] sameness is a prerequisite for [bioequivalence] and it is customary for the agency to

[73] Petition at 16-18 (citing Tables 1-3).

[74] See Petition at 18-19 (footnotes omitted) (citing Table 4).

[75] Petition at 19.

[76] Petition at 2 and 19.

[77] Petition at 1.

[78] Petition at 19.

[79] See Petition at 19-20.

[80] Petition at 20.

provide recommendations on [active ingredient] sameness in its product-specific BE guidances when [active ingredient] characterization or structure is a potential issue."[81]

B. Request Enhanced Bioequivalence Recommendations in the Draft Sacubitril/Valsartan PSG

Novartis lodges three chief complaints against the bioequivalence recommendations included in the Draft Sacubitril/Valsartan PSG and requests enhanced recommendations for any generic applicant seeking approval of a product referencing Entresto as the RLD.

1. Requests Measurements of Primary Active Metabolite

Novartis contends that the Draft PSG fails to account for sacubitrilat (LBQ657)—the active metabolite of sacubitril—as a necessary analyte that should be measured in the plasma for purposes of establishing bioequivalence to Entresto.[82] Novartis asserts that "LBQ657 is generated pre-systemically by first pass metabolism," asserting the following:

> The human small intestine and liver show extensive hydrolase activity attributed to carboxylesterase (CES) and demonstrate a role in first-pass metabolism. Novartis has conducted a study to determine the specific CES enzymes capable of hydrolyzing sacubitril to form the active metabolite, sacubitrilat. The study results indicate that human CES 1 was capable of hydrolysis of sacubitril to form sacubitrilat. The CES 1 family of enzymes are expressed predominantly in the liver. Accordingly, the pre-systemic conversion of sacubitril to sacubitrilat takes place primarily in liver during first-pass.[83]

Novartis contends that in such cases FDA may require the metabolite of a parent drug to be assessed.[84] Novartis further asserts that it has "consistently used sacubitrilat as one of the three drug related analytes . . . for bioanalytical assessment," "due to the dual mechanisms of action of [Entresto] and the nature of sacubitrilat as the therapeutic moiety for [neprilysin] inhibition, which directly contributes to the safety and efficacy of the drug product."[85] Novartis contends that FDA should require generic applicants to analyze sacubitril, valsartan, and the active metabolite sacubitrilat (LBQ657) for purposes of establishing bioequivalence to Entresto.

Novartis asks FDA to revise the Draft PSG to include "the primary active metabolite, sacubitrilat [(LBQ657)], as an additional analyte for purposes of establishing [bioequivalence]:"[86]

> [T]he [Draft Sacubitril/Valsartan PSG] should be revised to state that data for sacubitril, valsartan and sacubitrilat should be collected, analyzed and submitted. Individual and

[81] Petition at 2 and 3.

[82] Petition at 2.

[83] Petition at 21, footnote 49.

[84] Petition at 21-22 (footnote omitted).

[85] Petition at 22 (footnote omitted).

[86] Petition at 2, 3, and 21-22.

> mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}, should be submitted for LBQ657 (sacubitrilat), as well as sacubitril and valsartan. The data should be statistically analyzed using the 90% confidence interval approach, and bioequivalence established for each analyte.[87]

2. Request Relative Pharmacokinetic Measurements of Three Analytes

Novartis asserts that "[Entresto] relies on inhibition of neprilysin by sacubitril/LBQ657, and simultaneous AT1 receptor blockade by valsartan," such that "attention must be given to the relative [pharmacokinetics] of each of the three analytes to be measured for [bioequivalence] purposes."[88] According to Novartis, "[t]he relativity of the overlap in [pharmacokinetics] of the active constituents is recognized in the [FDA-approved labeling for Entresto], and no data exist supporting the effectiveness of a product in which the PK curves bear a different relationship to one another."[89]

Novartis asks FDA to revise the Draft PSG to include relative PK measurements:[90]

> [T]he Draft Guidance should be revised to recommend an analysis of the PK profile of sacubitril, LBQ657, and valsartan, relative to one another, for both the test and RLD product. The relative relationship among the curves for the generic should be the same as that of the RLD products. Accordingly, FDA should include a recommendation for ANDA sponsors to evaluate the relation between the PK curves of each analyte.[91]

3. Request for Additional In Vivo Bioequivalence Study

Novartis asserts that the Draft PSG "improperly provides for a waiver request of [in vivo] testing for the 24 mg/26 mg dosage strengths based in part on 'proportional similarity in the formulations of all strengths,'"[92] contending that the 24 mg/26 mg strength of Entresto "is not proportionally similar to the 49 mg/51 mg and 97 mg/103 mg strengths."[93] Novartis relies on a meaning of "proportionally similar" found in FDA's Draft ANDA BE Guidance[94]: "all active and inactive ingredients are in similar proportion between different strengths (e.g., a tablet of 50-

[87] Petition at 22.

[88] See Petition at 22.

[89] Petition at 23.

[90] Petition at 2, 3-4, and 22-23.

[91] Petition at 22-23. See also Petition at 2 and 3-4.

[92] See Petition at 2.

[93] Petition at 24.

[94] We note that Novartis's Petition cites the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013), which was revised by FDA in August 2021. However, the specific meaning of "proportionally similar" referenced in Novartis's petition was not revised in the August 2021 Draft ANDA BE Guidance.

mg strength has all the inactive ingredients—almost exactly half that of a tablet of 100-mg strength, and almost twice that of a tablet of 25-mg strength)."[95]

Novartis asserts that the 24 mg/26 mg strength tablet of Entresto "contains 25% active ingredient by weight," while the 49 mg/51 mg and 97 mg/103 mg strength tablets "contain 50% active ingredient by weight."[96] Novartis further notes that the 24 mg/26 mg strength tablet of Entresto is "the same size and weight as the 49/51 mg strength tablet."[97] Novartis contends that generic applicants should maintain the larger size of the 24 mg/26 mg strength tablet, which, according to Novartis, "means the proportionality requirement for the biowaiver will not be met."[98] Novartis also contends that "if the proportionality requirement is met, the proposed generic product will be significantly different in size."[99]

Novartis contends that "[d]ue to absence of proportional similarity between the 24/26 mg strength and the higher strengths of [Entresto], FDA must require an additional in vivo study to establish bioequivalence to the 24 mg/26 mg strength RLD tablet."[100] Novartis asks FDA to revise the Draft PSG to include such an additional in vivo study.[101]

III. DISCUSSION

We disagree with Novartis's contention that applicants should be required to establish active ingredient sameness to Entresto by demonstrating sacubitril and valsartan in ionic coordination with sodium with 1:1:3 stoichiometry. We also disagree that revised bioequivalence recommendations for sacubitril and valsartan oral tablets are necessary at this time. Lastly, we decline to revise the Draft Sacubitril/Valsartan PSG as requested in Novartis's Petition.

We discuss our reasoning below.

A. Proposed Generics Need Not Match the Coordinated Ionic Structure of the Active Ingredients in Entresto To Satisfy the Sameness of Active Ingredient(s) Requirement

We disagree that generic applicants should be required to establish active ingredient sameness to Entresto by demonstrating that their proposed products contain sacubitril and valsartan in ionic coordination with sodium with 1:1:3 stoichiometry. FDA has determined that Entresto contains sacubitril sodium and valsartan disodium, which exist in the form of a hemipentahydrate co-crystal. As noted above, FDA's position, reflected in the Co-Crystal Guidance, is that "[a] co-crystal that is composed of two or more [active ingredients] (with or without additional inactive

[95] See Petition at 23 (citation omitted).

[96] See Petition at 24.

[97] Ibid.

[98] Ibid.

[99] Ibid.

[100] See Petition at 23.

[101] Petition at 2, 3-4, and 23-25.

coformers) will be treated as a fixed-dose combination product and not a new single [active ingredient]."[102] Unlike what we would expect from a new single active ingredient in salt form, the adhesive forces between the two active ingredients comprising the Entresto co-crystal (i.e., the sodium salts of sacubitril and valsartan) are weak as well as non-covalent and non-ionic. As acknowledged by Novartis,[103] the Agency accordingly views Entresto as a fixed-combination of sacubitril sodium and valsartan disodium.[104]

For fixed-combination products, FDA generally requires generic applicants to demonstrate that the same chemical form of each individual active ingredient in the RLD product—e.g., as represented by their respective chemical formulas, United States Adopted Names, and the molecular structures (including salt forming counterions)—be present in the proposed generic product. Moreover, the Co-Crystal Guidance explains that "[f]rom a physical chemistry and regulatory perspective, co-crystals can be viewed as a special case of solvates and hydrates . . . ."[105] Active ingredients with the same chemical identity may exist in different physical forms, such as polymorphs, solvates, and hydrates. In general, these different physical forms do not bar a generic applicant from demonstrating active ingredient sameness.[106] Novartis's Petition does not provide, nor are we aware of, any data demonstrating that the physical form of the active ingredients in Entresto is known to impact the safe or effective use of the drug. In fact, there is no systemic exposure to the Entresto co-crystal, which dissociates in vivo to sacubitril and valsartan as stated in Entresto's labeling.[107] Absent a showing that the physical form of the Entresto co-crystal impacts the safe or effective use of the drug, FDA generally expects generic applicants to demonstrate "sameness" based on the identity of the individual active ingredients (sacubitril sodium and valsartan disodium) of Entresto. We therefore disagree with Novartis's assertion that "FDA cannot permit an ANDA based on a physical mixture of individual sodium salts . . . of sacubitril and valsartan."[108]

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[102] Co-Crystal Guidance at 3.

[103] See Petition at 8 ("[Entresto] was reviewed and approved as a combination of sacubitril and valsartan . . . ."); see also Petition at 14 ("Accordingly, under FDA's definition, LCZ696 is not a co-crystal, but nonetheless remains a combination of drug substances.").

[104] See, e.g., NDA 207620, Office Director Memo at 3.

[105] Co-Crystal Guidance at 2 (footnote omitted).

[106] See, e.g., Citizen Petition Responses at Docket Nos. FDA-2016-P-3418 and FDA-2008-P-0300.

[107] See Entresto Prescribing Information, 11 Description, 12.3 Pharmacokinetics (Apr. 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/207620s025,218591s000lbl.pdf.

[108] To support its argument that an ANDA containing a mixture of the active ingredients could not meet the requirements for approval, the Petition harks back to information Novartis needed to provide during the review of its NDA. Specifically, on page 12 of the Petition, the Petitioner states:

> [I]n a mid-cycle Information Request, FDA observed that the validation data in the NDA was deficient in that the identity test did not distinguish LCZ696 from a 1:1 mixture of sacubitril and valsartan. In response, Novartis informed FDA of the development of two additional identity tests, an FTIR and X-ray crystallography test, both of which have been validated to distinguish LCZ696 from the individual components . . . . The Novartis response satisfied the agency's request and confirmed, per the agency's inquiry, that the

As explained in section I of this response, in the 1992 preamble to the final rule implementing the Hatch-Waxman Amendments, FDA specifically rejected a suggestion to require that a proposed ANDA's active ingredients "exhibit the same physical and chemical characteristics . . . and that the stereochemistry characteristics and solid state forms of the drug have not been altered."[109] Instead, we have long adopted a flexible approach regarding the information we may consider regarding an ANDA establishing active ingredient sameness, stating that we would "consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity."[110] The Petitioner's contentions about what constitutes the "chemical structure" of Entresto's active ingredients,[111] and to which it argues an ANDA applicant must show sameness (i.e., the "complex with the same 1:1:3 sacubitril:valsartan:sodium stoichiometry that defines the chemical structure"[112] and the arrangement or ionic coordination of the molecules),[113] does not comport with this long-standing approach (see, e.g., footnote 10). Identity of active ingredients in a combination product is generally demonstrated through appropriate analytical testing to support sameness in the chemical structure of each individual active ingredient, which, FDA generally considers to be the entire molecule, or ion, including the portions of the molecule that cause the drug to be an ester or salt.[114] Generic applicants referencing Entresto as the RLD are required to submit, among other things, a full description of each drug substance, including its physical and chemical characteristics and the specifications necessary to ensure its identity, strength, quality, and purity.[115] The determination of chemical identity for an active ingredient may be elucidated through a large number of available orthogonal methods and includes a wide variety of chemical

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drug substances in the finished dosage form of the product exist as a specific complex. (Footnotes omitted.)

The Petition's contentions about the information Novartis needed to provide in the context of its NDA are not convincing with respect to the information that an ANDA applicant could use to demonstrate active ingredient sameness. Under § 314.50(d) (21 CFR 314.50(d)), an NDA must contain technical sections with sufficient detail to make a knowledgeable judgment about whether to approve the NDA; this includes a chemistry, manufacturing, and controls section that describes the composition, manufacture, and specification of the drug substance and of the drug product (see § 314.50(d)(1)). Information such as what Novartis had to show to address a deficiency regarding the validation data contained in its pending NDA and to support its labeling claims are distinct from, and do not necessarily inform, how a potential applicant for an ANDA would meet the statutory requirements to contain the same active ingredient(s).

[109] See the final rule "Abbreviated New Drug Application Regulations" (57 FR 17950 at 17958-17959, April 28, 1992).

[110] Ibid. at 17959.

[111] Petition at 8-14.

[112] Petition at 4 and 20.

[113] For example, Petition at 1 and 19.

[114] We note that proposed generic formulations of Entresto could violate the principles of active ingredient sameness if based on (1) a physical mixture of "other salts" of sacubitril or valsartan, (2) "sacubitril and valsartan as free acids," or (3) sacubitril and valsartan "in an anionic state in association with a metal or cation other than Na+" (see Petition at 2 and 19-20).

[115] See § 314.94(a)(9) (cross-referencing § 314.50(d)). See also FDA's guidance for industry *ANDA Submissions—Content and Format* (June 2019, Rev. 1) ("3.2.S.3.1 Contains an elucidation of the API structure and other characteristics.").

and spectroscopic methods. Methods to establish chemical identity are chosen based on their relevance to the anticipated structure of the active ingredient(s) used in the proposed generic drug product.

For the reasons discussed above, we deny Novartis's request that generic applicants be required to establish active ingredient sameness to Entresto by a showing that their proposed products contain sacubitril and valsartan in ionic coordination with sodium with 1:1:3 stoichiometry.[116] Rather, we generally expect ANDA applicants to demonstrate "sameness" based on the identity of the individual active ingredients of Entresto (i.e., sacubitril sodium and valsartan disodium). Because we disagree with Novartis's proposed "sameness" standard, we likewise decline to revise the Draft Sacubitril/Valsartan PSG in the manner requested by Novartis in its Petition.[117]

B. The Draft Sacubitril/Valsartan PSG Is Consistent With the Agency's Current Recommendations for Demonstrating Bioequivalence of Sacubitril and Valsartan Tablets

Novartis requests that FDA revise the Draft Sacubitril/Valsartan PSG to include: (1) LBQ657 as an additional analyte for purposes of establishing bioequivalence; (2) measurements to assess the pharmacokinetics of sacubitril, valsartan, and LBQ657 relative to one another; and (3) an additional in vivo study to establish bioequivalence between the 24 mg/26 mg strength tablet of

[116] The data presented in Novartis's Petition does not change our conclusion. We also note our disagreement with presentation of the data in Figures 5-7 of the Petition as being representative of a comparison between Entresto and a physical mixture of the two active ingredients in Entresto because sacubitril sodium and valsartan disodium were not used in the reported studies. The physical mixture used in Novartis's dissolution comparison consists of valsartan free acid and sacubitril calcium. As illustrated in Tables 1-3, at different pHs, the solubility of valsartan disodium is significantly higher than valsartan free acid. Sacubitril sodium has significantly higher solubility than sacubitril calcium at pH 6.8 and water. We believe the observed difference in dissolution profiles is likely due to the differences in solubility of these alternate salt forms rather than a difference between the Entresto co-crystal and a physical mixture of sacubitril sodium and valsartan disodium. In addition, we do not view the similar PK profiles of valsartan (103 mg) in Entresto and valsartan (160 mg) in Diovan presented in Table 4 to be a valid illustration that the valsartan in Entresto has better systemic exposure than valsartan disodium in a physical mixture with sacubitril sodium. The active ingredient in Diovan is valsartan free acid, which has a significantly lower solubility and slower dissolution profile than valsartan disodium. We believe those differences in salt forms contribute significantly to the observed differences in bioavailability and PK profiles.

[117] We note Novartis's assertion that "it is customary for the agency to provide recommendations on [active ingredient] sameness in its product-specific BE guidances when [active ingredient] characterization or structure is a potential issue" (Petition at 2; Ibid. at 20, footnote 43 (citations omitted)). Specific product recommendations may contain differing amounts of detail and background information depending on the product and will be revised as appropriate to ensure that the most up-to-date recommendations are available to the public. While FDA has on occasion included active ingredient sameness recommendations in some product-specific guidances, here, for the reasons discussed above in section III.A., the Agency does not agree with the Petition's assertion that "[active ingredient] characterization or structure is a potential issue" such that active ingredient sameness recommendations should be included in the Draft Sacubitril/Valsartan PSG. As described in our guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010), FDA develops product-specific bioequivalence recommendations based on its understanding of a variety of sources of information including the characteristics of the RLD, information derived from published literature, Agency research, and consultations within different offices in CDER, as needed, based upon the novelty or complexity of the bioequivalence considerations.

Entresto and the proposed generic at the same strength. For the reasons discussed below, Novartis's request is denied in all three respects.[118]

1. Testing of the Metabolite Sacubitrilat (LBQ657) Is Unnecessary To Demonstrate Bioequivalence

The Draft PSG recommends that an ANDA applicant conduct a PK BE study measuring both sacubitril and valsartan (but not the primary active metabolite of sacubitril, LBQ657) in plasma from subjects using its proposed generic product and the RLD to demonstrate bioequivalence. FDA generally recommends that generic applicants measure only the parent drug (the moiety released from the dosage form) rather than the metabolite during bioequivalence testing because the concentration-time profile of the parent drug is more sensitive to changes in formulation than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.[119]

FDA believes that the parent drug in the dosage form should be measured in biological fluids collected in BE studies unless accurate assay quantitation of the parent drug is not possible using state-of-the-art technology.[120] Novartis does not suggest that sacubitril cannot be measured accurately; in fact, Novartis implicitly concedes that it is measurable by asking for BE testing for sacubitril and its primary active metabolite. Under such circumstances, FDA generally recommends that a primary metabolite be measured only if it is both formed substantially through pre-systemic metabolism and contributes significantly to the safety and efficacy of the product.[121] Measuring the parent drug alone may be sufficient for BE purposes if the metabolite is mainly formed in the liver, after absorption has already occurred (as opposed to in the gut wall where any formulation-effect may not be fully detected by only monitoring the parent drug).

We note that, in the absence of PK data following intravenous administration of Entresto, sacubitril, or LBQ657, the extent of first-pass metabolism of sacubitril to form LBQ657 cannot be conclusively determined. However, based on our review of information found in the Clinical Pharmacology and Biopharmaceutics Review(s) for Entresto,[122] the published literature,[123] as well as other information available to the Agency, we believe it is reasonable to assume that sacubitril undergoes first-pass metabolism in the liver.[124] Although PK data on LBQ657 could

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[118] We note that Novartis's request to revise the Draft Sacubitril/Valsartan PSG to reflect Novartis's proposed "sameness" standard is addressed in section III.A, above.

[119] See discussion at section I.B.3., supra.

[120] Ibid.

[121] Ibid.; see also Draft ANDA BE Guidance at 15. As noted above, for purposes of bioequivalence determinations, measurement of a parent drug generally provides more relevant information on formulation differences than measurement of a metabolite, which will reflect metabolite formation, distribution, and elimination.

[122] See NDA 207620, Clinical Pharmacology and Biopharmaceutics Review(s) at 19-22, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ClinPharmR.pdf.

[123] J Shi, X Wang, J Nguyen, A Wu, B Bleske, and HJ Zhu, April 2016, Sacubitril is Selectively Activated By Carboxylesterase 1 (CES1) in the Liver and the Activation is Affected by CES1 Genetic Variation, Drug Metabolism and Disposition, 44(4):554-559.

[124] We note Novartis's agreement with this assumption (see Petition at 21, footnote 49 ("Accordingly, the pre-systemic conversion of sacubitril to sacubitrilat takes place primarily in liver during first-pass.")).

be used to provide supportive evidence of a comparable therapeutic outcome, we believe that measuring the parent drug sacubitril (rather than both sacubitril and its primary metabolite LBQ657) in a bioequivalence study as described in the Draft PSG is the most accurate, sensitive, and reproducible approach for purposes of evaluating bioequivalence because it is a direct measure for detecting possible formulation differences.[125] Moreover, Novartis's Petition does not provide, nor are we aware of, any data demonstrating that a BE determination that does not include measurements of the sacubitril metabolite LBQ657 would necessarily fall short of the Agency's statutory and regulatory requirements for establishing bioequivalence. Rather, it is appropriate for the Agency to examine the data associated with each application on a case-by-case basis to determine whether it meets the Agency's standards for bioequivalence.

Accordingly, after reviewing the information submitted with Novartis's Petition and other information available to the Agency, we deny Novartis's request to revise the Draft Sacubitril/Valsartan PSG to include the primary active metabolite of sacubitril, LBQ657, as an additional analyte for purposes of establishing bioequivalence to Entresto.

2. Relative Pharmacokinetic Measurements of Sacubitril, LBQ657, and Valsartan Are Unnecessary To Demonstrate Bioequivalence

We disagree with Novartis that the Draft PSG should recommend measurements to assess the pharmacokinetics of sacubitril, LBQ657, and valsartan relative to one another, for both the proposed generic product and Entresto. The reasons for why PK measurements of LBQ657 are not required for purposes of establishing bioequivalence to Entresto, as explained above, apply equally to Novartis's request for relative PK measurements, including LBQ657. Moreover, in assessing bioequivalence between a test product and an RLD that is a fixed-combination drug, the Agency generally does not assess the relation between PK curves of the individual active ingredients in the same product. Rather, the Agency evaluates PK parameters (e.g., C_{max} and AUC) for each active ingredient in the test product, compared to the PK parameters of each corresponding active ingredient in the RLD. For immediate-release, fixed-combination drugs such as Entresto, if each active ingredient in the test product demonstrates bioequivalence to each corresponding active ingredient in the RLD, then the relation between the PK curve of the individual active ingredients is inferred to be the same between the proposed generic product and the RLD. The Agency's general practice also includes comparing PK profiles (e.g., visual check and T_{max} comparison) of each active ingredient between the generic and RLD.

Entresto is recommended to be administered as a twice-daily dosing regimen that is likely to be used over a long period of time as a chronic therapy in chronic heart failure patients. As reported in Entresto's labeling, following oral administration, peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. Following twice-daily dosing, steady state concentrations of sacubitril, LBQ657, and valsartan are reached in 3 days.[126] Upon repeat administration following chronic dosing, there is significant overlap in the PK profiles of the analytes (sacubitril, LBQ657, and valsartan). Inhibition of neprilysin enzyme by LBQ657 and blocking of angiotensin receptor by valsartan, together contribute to the

[125] See section I.B.3., supra.

[126] See Entresto Prescribing Information, 12.3 Pharmacokinetics (Apr. 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/207620s025,218591s000lbl.pdf.

therapeutic activity of Entresto; however, we believe that any minor difference in the relative PK curves of sacubitril, LBQ657, and valsartan at steady state cannot be expected to have a significant effect on the safety and efficacy of Entresto following repeated oral administration every 12 hours.[127]

Accordingly, we deny Novartis's request that the Agency revise the Draft Sacubitril/Valsartan PSG to include a recommendation "to evaluate the relation between the PK curves" of sacubitril, LBQ657, and valsartan.

3. A Waiver of In Vivo Bioequivalence Testing Can Be Granted for Lower Strengths Because Entresto Exhibits Dose Proportional Exposure In Vivo

After reviewing the information submitted with Novartis's Petition, along with other information available to the Agency, we deny Novartis's request to add an additional in vivo study to the Draft PSG.

As explained above, under 21 CFR 320.22(d), FDA will waive the requirements for the submission of evidence obtained in vivo demonstrating the bioequivalence of a drug product if any one of several listed criteria is satisfied. Consistent with this regulation, an applicant seeking approval of an ANDA that references Entresto may justify a waiver of the requirement for submission of in vivo bioequivalence data if:

> The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer [i.e., the ANDA applicant] has obtained approval [or is obtaining approval] and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) are met:
>
> (i) The bioavailability of this other drug product has been measured;
>
> (ii) Both drug products meet an appropriate in vitro test approved by FDA; and
>
> (iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.[128]

The Draft Sacubitril/Valsartan PSG recommends waiver of in vivo testing for the 24 mg/26 mg strength tablet based on: (i) acceptable bioequivalence studies on the 97 mg/103 mg strength, (ii) comparable dissolution testing on all strengths, and (iii) proportional similarity in the formulations of all strengths. Novartis's Petition argues that it is inappropriate for the Draft Sacubitril/Valsartan PSG to include a waiver recommendation of in vivo bioequivalence testing for the 24 mg/26 mg dosage strength because the 24 mg/26 mg strength of Entresto is not proportionally similar to the 49 mg/51 mg and 97 mg/103 mg strengths, and thus ANDA applicants will be unable to demonstrate proportional similarity in the formulations of all

[127] We note that the Agency did not rely upon the relative relationship among the PK curves of sacubitril, LBQ657, and valsartan in determining the safety or effectiveness of Entresto.

[128] See 21 CFR 320.22(d)(2); see also Draft ANDA BE Guidance at 10.

strengths.[129] The first step in determining proportional similarity typically is to determine whether all strengths of the RLD are proportionally similar in their active and inactive ingredients (also referred to as *compositionally proportional*). We agree that the 24 mg/26 mg strength of Entresto is not compositionally proportional to the 49 mg/51 mg and 97 mg/103 mg strengths in its active and inactive ingredients for the reasons stated in Novartis's Petition.[130] However, even if all strengths of the RLD are not compositionally proportional, proportional similarity among different strengths can still be concluded if there is suitable in vivo evidence of dose proportionality.

In other words, the meaning of *proportional similarity* is not limited to compositional proportionality of active and inactive ingredients as Novartis suggests.[131] Rather, active and inactive ingredients that are not in similar proportion between different strengths can still be considered proportionally similar with adequate justification.[132]

In developing the current bioequivalence recommendations in the Draft Sacubitril/Valsartan PSG, the Agency evaluated formulation and dissolution data, information from in vivo studies, including bioavailability/bioequivalence studies, and other relevant data. Although Entresto does not show compositional proportionality of active and inactive ingredients across all three of its strengths, evidence from in vivo PK studies included in the original NDA showed that the different strengths of Entresto result in dose proportional exposure in vivo. The Agency's conclusion that the strengths of Entresto exhibit dose proportional exposure is supported by the Clinical Pharmacology and Biopharmaceutics Review(s)[133] as well as Entresto's labeling, which states that "[t]he pharmacokinetics of sacubitril, LBQ657, and valsartan were linear over an [Entresto] dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan."[134] As Novartis's own studies demonstrate, the lack of compositional proportionality between different strengths of Entresto does not mean that the different strengths do not exhibit dose proportional exposure. The lack of compositional proportionality merely means that we may not consider the strengths of Entresto dose proportional absent in vivo data. In this case, Novartis provided such evidence in the form of an in vivo study when it submitted its NDA. When dose proportional exposure is demonstrated for the RLD in vivo, like it has been for Entresto, it supersedes any inference that the strengths are not dose proportional based on lack of proportional similarity of active and inactive ingredients. In other words, when an RLD formulation shows dose proportional exposure in vivo across its strengths, then in vivo testing of other strengths of a proposed generic product can be waived based on dissolution tests and an acceptable in vivo study.

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[129] Petition at 23-25.

[130] See Petition at 24.

[131] Draft ANDA BE Guidance at 10-11.

[132] Ibid. at 11.

[133] See NDA 207620, Clinical Pharmacology and Biopharmaceutics Review(s) at 19.

[134] Entresto Prescribing Information, 12.3 Pharmacokinetics (Apr. 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/207620s025,218591s000lbl.pdf.

Considering the above discussion, we believe that the dose proportional exposure exhibited by the three strengths of Entresto provides adequate justification for concluding that proportional similarity exists in the formulations of all strengths of Entresto. Accordingly, we maintain the Draft Sacubitril/Valsartan PSG's recommendations for a waiver of in vivo bioequivalence testing of the 24 mg/26 mg strength and deny Novartis's request to add an in vivo bioequivalence study on the 24 mg/26 mg strength to the recommendations in the Draft PSG.[135]

IV. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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Date: 2024.05.28 15:41:52 -04'00'

Patrizia Cavazzoni, M.D.
Director
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[135] In connection with the Petitioner's request that the Draft PSG recommend an in vivo test to demonstrate bioequivalence, Novartis makes note of—and suggests that proposed generic drugs should maintain—the larger physical size of the Entresto tablet, 24/26 mg. As support, Novartis cites an excerpt from the FDA guidance for industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (Oct. 2022). We note that the Petition cites to the 2015 version of the guidance, which was revised in 2022, but includes the same excerpt cited by Novartis. The guidance, however, pertains to swallowing difficulties posed by larger tablets and, accordingly, recommends that applicants design and develop generic drugs "to minimize swallowing difficulties, which can encourage and improve patient compliance with medication regimens" (Ibid. at 4). The considerations in the guidance are inapposite to tablets smaller in size compared to the RLD, as Novartis's Petition appears to contemplate; and, overall, the acceptability of a generic drug's physical attributes would be determined in the context of the review of a specific application.