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CITIZEN PETITION

Novartis Pharmaceuticals Corporation (Novartis) respectfully submits this citizen petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law. Novartis is the sponsor of ENTRESTO® (sacubitril/valsartan), which is the reference listed drug (RLD) and reference standard (RS) for purposes of approving a generic version of ENTRESTO under section 505(j) of the Food, Drug, and Cosmetic Act (FDCA). As discussed in detail below, we respectfully request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application (ANDA) for a generic version of ENTRESTO.

The new drug application (NDA) for ENTRESTO (sacubitril/valsartan) oral tablets was approved on July 7, 2015, and received 5-year new chemical entity (NCE) exclusivity. Accordingly, the earliest date on which an ANDA could be submitted to FDA for review is July 7, 2019, and final approval of an ANDA would not reasonably be anticipated until at least January 2023 (accounting for expected patent litigation). This citizen petition raises important issues regarding the chemical identity of the active ingredients in ENTRESTO, and the data needed to demonstrate bioequivalence to ENTRESTO. Novartis is petitioning at this time well before any ANDA may be submitted to FDA, and well before any final ANDA approval, to allow the agency maximum time to consider the petition.

ENTRESTO is approved 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. It is designed as a dual action drug product comprising a neprilysin inhibitor, sacubitril, and an angiotensin II receptor blocker (ARB), valsartan. ENTRESTO was reviewed and approved as a combination of two drug substances. Unlike most combination drug products, which contain, for example, a physical mixture of two or more active ingredients, the active ingredients in ENTRESTO are present in the finished dosage form as 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. That is, the two active ingredients that form the combination co-exist in ENTRESTO in a 1:1 molar ratio, together with coordinated Na^+ , as a complex.

For a drug product to be approved under an ANDA, it must include active ingredients (active pharmaceutical ingredients, APIs) that are “the same as” the RLD. This requires, among other things, the active ingredients in the proposed generic drug to have the same chemical structure as the active ingredients in the RLD. Thus, an ANDA that is based on, *e.g.*, sacubitril and valsartan as free acids, or in an anionic state in association with a metal or cation other than Na^+ , would violate principles of ANDA sameness. Similarly, FDA cannot permit an ANDA based on a physical mixture of individual sodium salts (or other salts) of sacubitril and valsartan. FDA must require that for a generic version of ENTRESTO to be approved under an ANDA, sponsors of generic versions of ENTRESTO must present the active ingredients in the same chemical structure as in the RLD.

In 2016, the Food and Drug Administration (FDA) issued draft product-specific bioequivalence (BE) recommendations for sacubitril/valsartan generic oral tablets (the Draft Guidance).¹ FDA’s Draft Guidance for sacubitril/valsartan fails to include appropriate recommendations on “API sameness.” Specifically, it does not provide instructions to ensure that generic versions of ENTRESTO contain the same active ingredients as the RLD, namely, sacubitril and valsartan in coordination with Na^+ in the appropriate stoichiometry ratio. API sameness is a prerequisite for BE and it is customary for the agency to provide recommendations on API sameness in its product-specific BE guidances when API characterization or structure is a potential issue.

The Draft Guidance includes three additional deficiencies. First, the Draft Guidance 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 conducting bioequivalence studies. Second, because ENTRESTO relies on inhibition of neprilysin by sacubitril/LBQ657, and simultaneous AT1 receptor blockade by valsartan,² attention must be given to the relative pharmacokinetics (PK) of each of the three analytes to be measured for BE purposes. ANDA sponsors should be instructed to assess the PK of each analyte relative to one another to ensure comparability between test product and the RLD product. Third, the Draft Guidance 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,”³ despite the fact that the 24/26 mg strength and the higher strengths of ENTRESTO lack proportional similarity.

¹ Food and Drug Administration, Draft Guidance on Sacubitril; Valsartan (Apr. 2016), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495419.pdf> (Draft Guidance (on sacubitril/valsartan)).

² See, *e.g.*, Package Insert, 12.1 Mechanism of Action (“The cardiovascular and renal effects of ENTRESTO in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan.”).

³ Draft Guidance (on sacubitril/valsartan), *supra* note 1.

Novartis submitted comments to FDA in response to the Draft Guidance, alerting FDA of the need to amend the guidance.⁴ FDA has gone through at least six cycles of product-specific BE guidance updates since Novartis submitted its comments but with no further revision to the ENTRESTO Draft Guidance.⁵ Accordingly, we are submitting this citizen petition to formally request under 21 CFR 10.30 that FDA revise the Draft Guidance to include API sameness criteria and other requested changes.⁶ Irrespective of whether FDA chooses to revise the Draft Guidance, FDA must require generic drug applicants to establish that the generic product contains a complex with the same 1:1:3 sacubitril:valsartan:sodium stoichiometry that defines the chemical structure of sacubitril and valsartan as they exist in ENTRESTO.

ACTIONS REQUESTED

Novartis respectfully requests that the Commissioner take the following actions:

- (1) Require ANDAs that reference ENTRESTO to demonstrate API 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 Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds;
- (3) Further revise the Draft Guidance to include:

⁴ Novartis Comments, Docket. No. FDA-2007-D-0369-0437, <https://www.regulations.gov/document?D=FDA-2007-D-0369-0437>.

⁵ See 84 FR 6005 (Feb. 25, 2019); 83 FR 67292 (Dec. 28, 2018); 83 FR 61388 (Nov. 29, 2018); 83 FR 50943 (Oct. 10, 2018); 83 FR 46745 (Sept. 14, 2018); 83 FR 34851 (July 23, 2018).

⁶ Despite an open public docket for the development of a bioequivalence guidance, FDA has previously withdrawn or revised draft bioequivalence recommendations based on substantive issues raised in a citizen petition. *See, e.g.*, FDA Citizen Petition Response, Docket. No. FDA-2016-P-2781-0006 (Feb. 10, 2017) at 15 (stating that a Draft Bioequivalence Guidance on Difluprednate “is being revised to include the recommendation that the applicant measure both the parent drug . . . and the active metabolite . . .”); FDA Citizen Petition Response, Docket. No. FDA-2016-P-1873-0007 (Nov. 23, 2016) at 8 (“FDA agrees with your request and has revised the product-specific recommendations set forth in the guidance to include recommendations for demonstrating bioequivalence . . .”).

- a) the primary active metabolite, sacubitrilat, as an additional analyte for purposes of establishing BE;
- b) measurements to assess the PK of each analyte relative to one another to ensure comparability between test product and the RLD product; and
- c) an additional *in vivo* study to establish bioequivalence between the RLD 24 mg/26 mg strength tablet, and the generic counterpart at the same dose strength.

STATEMENT OF GROUNDS

I. BACKGROUND

A. ENTRESTO (sacubitril/valsartan)

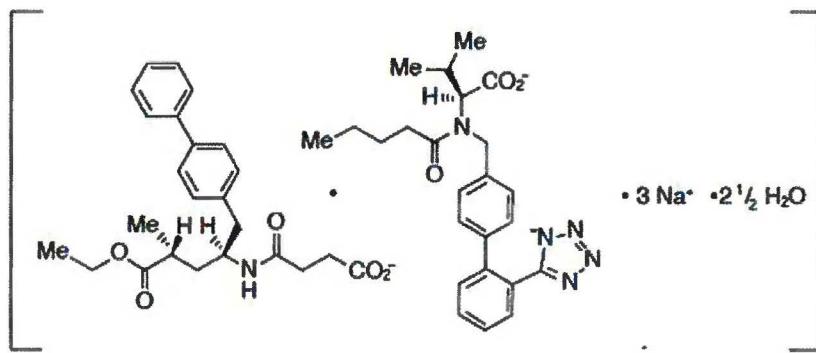
ENTRESTO (sacubitril/valsartan) is a combination of sacubitril and valsartan indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.⁷ It is available in strengths of 24/26 mg, 49/51 mg, and 97/103 mg.⁸

ENTRESTO inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657 (sacubitrilat), the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via the action of the angiotensin II receptor blocker (ARB), valsartan.⁹ Chemically, ENTRESTO contains a complex (also referred to as LCZ696) comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. The empirical formula is C₄₈H₅₅N₆O₈Na₃•2.5 H₂O; its molecular mass is 957.99; and the schematic structural formula is:

⁷ Package Insert, 1 Indication.

⁸ *Id.* at 3 Dosage Forms and Strengths.

⁹ *Id.* at 12.1 Mechanism of Action.



The safety and effectiveness of ENTRESTO was established in the PARADIGM-HF pivotal study, a multinational, randomized, double-blind trial comparing ENTRESTO and enalapril in 8,442 adult patients with symptomatic chronic heart failure and reduced ejection fraction (left ventricular ejection fraction $\leq 40\%$).¹⁰ PARADIGM-HF demonstrated that ENTRESTO was superior to enalapril in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis. The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization. ENTRESTO also improved overall survival, which was driven by a lower incidence of cardiovascular mortality.¹¹

B. FDA's Draft Guidance for sacubitril/valsartan for ANDA submissions

The Draft Guidance for sacubitril/valsartan recommends two bioequivalence studies: (1) a fasting study with a single-dose, two-way crossover *in vivo* design with the 97/103 mg strength tablet, in healthy males and non-pregnant females in the general population; and (2) a fed study with a single-dose, two-way crossover *in vivo* design with the 97/103 mg strength tablet, in healthy males and nonpregnant females in the general population. The Draft Guidance states that the analytes to measure should be sacubitril and valsartan in plasma. The Draft Guidance also provides for a waiver request of *in vivo* testing on the 24/26 mg and 49/51 mg strengths based on acceptable bioequivalence studies on the 97/103 mg strength, comparable dissolution testing on all strengths, and proportional similarity in the formulations of all strengths.

Notably, the Draft Guidance fails to include instructions or recommendations to ensure that generic versions of ENTRESTO will contain the same active ingredients as the RLD.

¹⁰ *Id.* at 14 Clinical Studies.

¹¹ *Id.*; see also McMurray, J., et al., Angiotensin-neprilysin inhibition versus enalapril in heart failure, NEJM (2014) 371: 993-1004 (Tab 1).

II. ARGUMENT

A. To establish “API sameness,” sponsors of generic versions of ENTRESTO must present the active ingredients in the same chemical structure as in the RLD

1. Framework for ANDA approval and API sameness

Under the FDCA, an applicant submitting an ANDA avoids conducting clinical studies to establish safety and effectiveness by relying instead on FDA’s previous finding of safety and effectiveness for a reference product. To do so, the ANDA applicant must show, among other things, that the active ingredient of the proposed generic “is the same as that of the listed drug” or the RLD.¹² By regulation, FDA has defined “same as” to mean “identical in active ingredient(s).”¹³ While the FDCA does not describe the amount or type of data that are required to show that two active ingredients are “the same,” FDA interprets the statute to prohibit an ANDA from including clinical investigations designed to study the safety or effectiveness of the proposed generic drug product.¹⁴ Additionally, where there are differences in molecular structure between the proposed generic product and the reference product, such as containing different salts or esters of the active ingredients in the listed drug, an ANDA is not permitted. Instead, the sponsor must submit its application as an NDA under section 505(b) of the FDCA.

This standard for sameness is also memorialized in FDA’s own regulations with respect to sponsors seeking approval of “pharmaceutically equivalent” generic drug products. Specifically, pharmaceutical equivalents are defined, in relevant parts, to mean drug products “that contain identical amounts of the identical active drug ingredient[.]” The regulations explicitly clarify that an “identical active drug ingredient” is “the same salt or ester of the same therapeutic moiety.”¹⁵ Meanwhile, the therapeutic or “active moiety” is “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or

¹² 21 USC 355(j)(2)(A)(ii); 21 CFR 314.92(a)(1); *see also* 21 CFR 314.94(a)(5) (ANDA must contain “information to show that the active ingredient is the same as that of the [RLD]”).

¹³ 21 CFR 314.92(a)(1). This standard is in contrast to the standard adopted by Congress for the approval of biosimilars under section 351 of the Public Health Service Act. Rather than adopting a sameness standard, modeled on the standard in section 505(j) of the FDCA, Congress specified that a proposed biosimilar must be shown to be “highly similar” to the reference product with no “clinically meaningful differences” in the safety, purity and potency. A showing that the active ingredient of a proposed generic is highly similar to the RLD would not meet the statutory standard under section 505(j) of the FDCA.

¹⁴ 57 FR 17950, 17953 (Apr. 28, 1992) (“[T]he act permits ANDAs only for duplicate and related versions of previously approved drug products. The ANDA applicant relies on a prior Agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. If investigations on a drug’s safety or effectiveness are necessary for approval, an ANDA is not permitted.”).

¹⁵ 21 CFR 314.3(b); 54 FR 28872, 28881 (July 10, 1989).

coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.”¹⁶ Accordingly, the active ingredient of a drug product “includes the appended portions of the molecule that make it a particular salt or other noncovalent derivative or ester.”¹⁷

FDA has also explained that for purposes of ANDA approval, “if the proposed drug contained [for example] a different salt or ester of the active ingredient in the listed drug, the proposed drug product would not be identical to the active ingredient in the listed drug, and could not, therefore, be approved in an ANDA.”¹⁸ The active ingredient of a drug product therefore includes the specific salt, ester, or, in some cases, the specific complex present in the drug product.¹⁹ It is further established that “sameness” of active ingredients under the regulations means the same chemical substances as they exist in the finished dosage form of the drug product prior to administration.²⁰

The legal requirement that the active ingredients in generic drugs must have the same chemical structure as the active ingredients in the RLD is distinct from FDA’s recognition that generic drugs may present the active ingredient in a different solid state form, or with different waters of hydration. FDA has concluded that “differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals.”²¹ According to FDA, “[p]olymorphic forms of a drug substance differ in internal solid-state structure, *but not in chemical structure.*”²² Different polymorphic forms, or even different solvate and hydrate forms of an active ingredient, do not preclude ANDA approval because, under the agency’s framework, these types of differences do not pertain to the chemical structure of the active ingredient.²³ As the agency has explained:

FDA has long regarded chemical structure as being fundamental to the identity of an active ingredient. Consequently, FDA regards different salts and esters of the same therapeutic moiety as pharmaceutical alternatives rather than pharmaceutical equivalents. On the other hand, different polymorphs of an active ingredient that

¹⁶ 21 CFR 314.3(b).

¹⁷ MAPP 5018.2 (Nov. 4, 2015) at 9.

¹⁸ 54 FR 28881.

¹⁹ See, e.g., Sodium ferric gluconate complex.

²⁰ 54 FR 28881.

²¹ Guidance for Industry – ANDAs: Pharmaceutical Solid Polymorphism (July 2007) at 5.

²² Id. (emphasis added).

²³ Id. at 6.

have the same primary chemical structure (the differences are in physical form) are considered pharmaceutical equivalents....²⁴

Thus, notwithstanding different physical or polymorphic forms, or even hydrated or solvated forms of an active ingredient, the *chemical structure* of each active ingredient in the finished dosage form of a proposed generic must be identical to the *chemical structure* of each active ingredient in the RLD.

2. *ENTRESTO contains sacubitril and valsartan in a defined chemical structure*

a. Chemical structure and identity

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 API sameness under FDA's established framework.

Specifically, spectroscopic studies show that ENTRESTO contains a complex of two drug substance-anions, sacubitril and valsartan, with ionic interactions with coordinated sodium cations. Within the structure, the sodium ions are coordinated by oxygen ligands derived from 12 negatively charged carboxylate groups and 18 carbonyl groups of both the sacubitril and valsartan components. In addition to the ionic bonds between the carboxylate groups and the sodium cations, the amide carbonyl groups coordinate to sodium ions. In contrast, the tetrazole rings of valsartan do not bind directly to sodium, but instead form a hydrogen bond to the amide NH of sacubitril, along with hydrogen bonds with the water molecules, which in turn form part of the coordination polyhedral of the sodium ions.²⁵

These chemical arrangements are so efficient that all carbonyl and carboxy oxygen atoms of valsartan and sacubitril are associated with multiple sodium ions. That is, all ligands coordinate

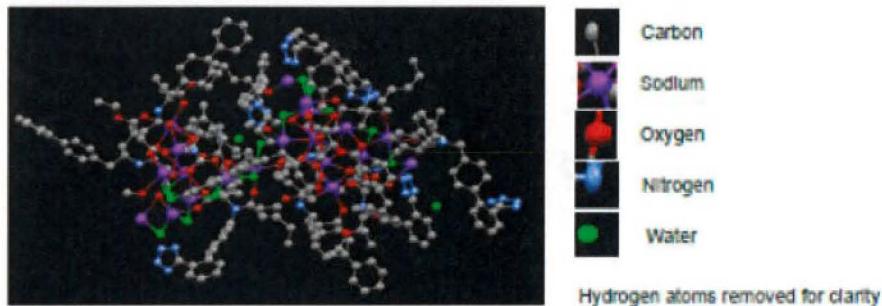
²⁴ FDA Citizen Petition Response, Docket Nos. 00P-1550/CP1 and 01P-0428/CP1 (Feb. 15, 2002) (Consolidated CP Response) at 28 (citations omitted). See also *id.* at 29 ("for the purposes of generic drug approvals, it is appropriate for FDA to treat salt/ester variations differently from variations in crystallinity because differences in chemical structure are more fundamental than physical form variations.").

²⁵ See Feng, L., et al., LCZ696: A dual acting supramolecular complex, Tetrahedron Letters (2012) 53: 275-276 (Tab 2).

to the sodium ions by oxygen atoms, derived from the carboxylate groups and the carbonyl groups of both sacubitril and valsartan. The 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.

The single X-ray structure reveals the efficiency of these arrangements, showing penta- and hexa-coordinated sodium ions as integral elements of the complex, with specific ionic interactions. All sacubitril-valsartan pairs have unique distributions of close contacts of less than 3Å, wherein each sacubitril molecular entity has six to eight close contacts with sodium, while each valsartan molecular entity has two to six close contacts with sodium. With respect to the two drug substance-anions, sacubitril and valsartan, twelve sodium ions coordinate to both sacubitril and valsartan, while four sodium ions associate exclusively with the sacubitril molecular component, and two sodium ions are associated exclusively with the valsartan molecular component. See Figure 1 below, depicting the structure of the supramolecular complex.

Figure 1: Asymmetric unit of the sacubitril/valsartan complex in LCZ696²⁶



Crystalline network bonding

Non-covalent Bonding:

- Ionic bonding: sacubitril and valsartan anions contact with sodium cations
- Hydrogen-bonding interactions: involving sacubitril anions and valsartan anions and water molecules
- Coordination bonding

Accordingly, ENTRESTO is recognized in the FDA-approved labeling as containing a complex of the active ingredients sacubitril and valsartan in their anionic forms, and sodium cations in the molar ratio of 1:1:3, respectively.²⁷ During earlier stages of review, FDA described this complex as “akin to a drug substance salt form where the counter ion plays a role in pharmacological activity.”²⁸

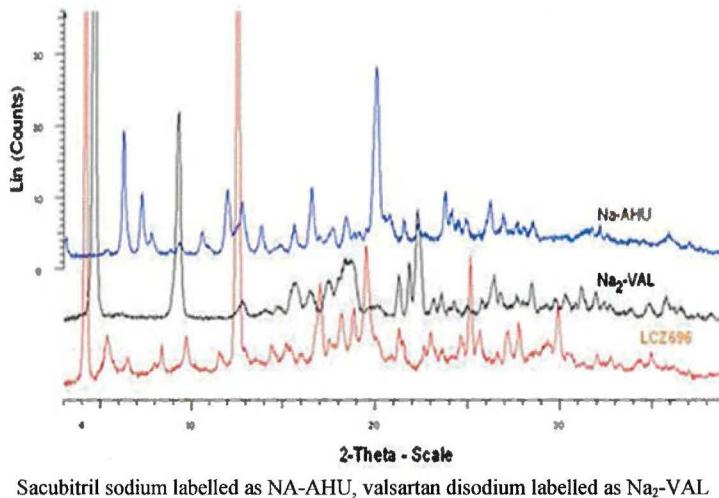
²⁶ *Id.*

²⁷ See, e.g., Package Insert, 11 Description (“ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations and water molecules in a ratio of 1:1:3:2.5.”).

²⁸ Type B Pre-NDA Meeting, Minutes, July 14, 2014 (on file at FDA).

In addition to X-ray crystallography to elucidate the chemical structure, Novartis conducted spectroscopic studies using X-ray powder diffraction spectroscopy, solid state NMR spectroscopy and IR spectroscopy. Novartis conducted these studies, using these methods, to demonstrate how sacubitril and valsartan in LCZ696 have distinct chemical structure that is different from a physical mixture of the individual sodium salts of sacubitril and valsartan (sacubitril sodium and valsartan disodium). The XRPD patterns of LCZ696, sacubitril sodium and valsartan disodium are presented in Figure 2. Next, Figure 3a shows the ^{13}C -NMR spectrum for LCZ696. This is contrasted with the same spectrum for a 1:1 mixture of sacubitril sodium and valsartan disodium in Figure 3b. Lastly, the ATR-FTIR spectra of LCZ696, sacubitril sodium and valsartan disodium are presented in Figure 4.

Figure 2: XRPD patterns of LCZ696-ABA, sacubitril sodium and valsartan disodium



Sacubitril sodium labelled as NA-AHU, valsartan disodium labelled as Na₂-VAL

Figure 3a: Solid state ^{13}C -NMR spectrum for LCZ696

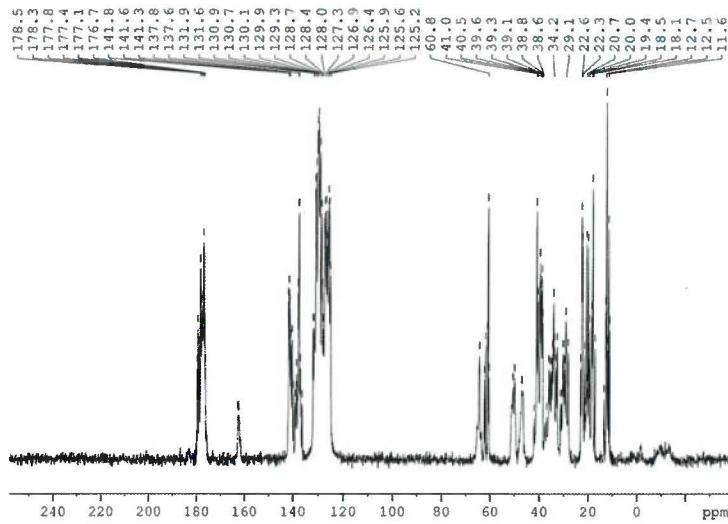


Figure 3b: Solid state ^{13}C -NMR spectrum for a 1:1 mixture of sacubitril sodium and valsartan disodium

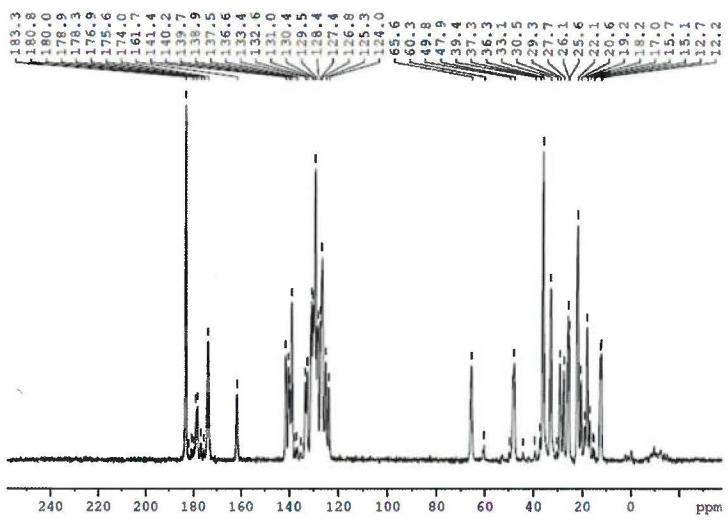
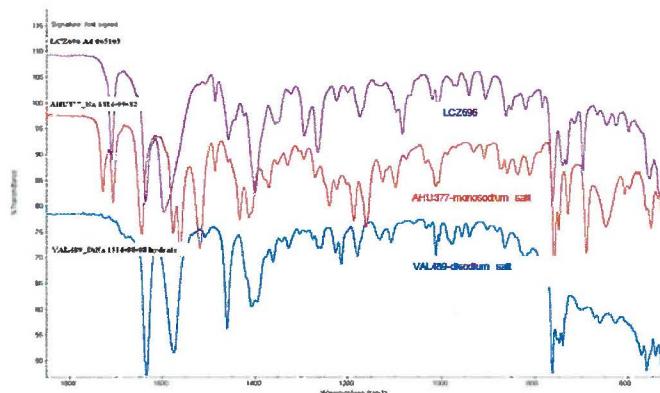


Figure 4: ATR-FTIR spectra of LCZ696-ABA, sacubitril sodium and valsartan disodium



Sacubitril sodium labelled as AHU377-monosodium salt, valsartan disodium labelled as VAL489-disodium salt

These data show that LCZ696 is distinct from a physical mixture of the individual sodium salts of sacubitril and valsartan. Indeed, in 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.²⁹ 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, sacubitril and valsartan.³⁰ The Novartis response satisfied the agency's request and confirmed, per the agency's inquiry, that the drug substances in the finished dosage form of the product exist as a specific complex.

In Pre-NDA communications, the agency also referred to the complex of LCZ696 as a "co-crystal" and as a "drug product intermediate," concluding that the active drug substances for purposes of NDA review would be sacubitril and valsartan.³¹ In doing so, the agency recognized both the specificity and the complexity of the chemical structure of sacubitril and valsartan, as they exist in LCZ696. For example, in the June 25, 2014, Pre-NDA meeting, FDA and Novartis discussed a number of confounding chemistry, manufacturing, and controls (CMC) issues, and, in particular, how to control the active substances, which are present as non-isolated, ionic components within the LCZ696 complex. Sacubitril and valsartan are not isolated and controlled in the manufacture of the finished drug product. Rather, drug substance controls are imposed primarily at the level of the LCZ696 complex, as agreed to by FDA.

²⁹ NDA 207620, Mid-Cycle Information Request, February 19, 2015 (on file at FDA).

³⁰ Novartis Response to Mid-Cycle Information Request, March 11, 2015 (on file at FDA).

³¹ Type B Pre-NDA Meeting, Minutes, July 14, 2014 (on file at FDA).

In reaching this position, the agency invoked the 2013 version of the guidance document, “Regulatory Classification of Pharmaceutical Co-Crystals,” then in effect, for pragmatic reasons to facilitate CMC review and reach consensus on the appropriate drug substance controls. As stated by FDA,

[t]hat Guidance is written for API-excipient co-crystals, but describes how the co-crystal is considered a drug product intermediate and not a drug substance or NME. We acknowledge that the sacubitril-valsartan co-crystal is isolated from the non-isolated sacubitril drug substance. We consider your co-crystal to be a drug product intermediate and acknowledge that the co-crystal is used in the drug product manufacturing process to determine the amount of the two drug substances charged for formulation. Your situation is more akin to a drug substance salt form where the counter ion plays a role in pharmacological activity. As such, while the sacubitril is not isolated and controlled prior to co-crystal formation, we will accept control over the co-crystal in lieu of individual controls over sacubitril and valsartan at the drug substance level.³²

While FDA used the co-crystal guidance to describe LCZ696 and facilitate the CMC discussions, the term “co-crystal” was used informally, with the agency acknowledging that LCZ696 is more like “a drug substance salt form.”³³ Indeed, under the terms of the final 2013 version of the co-crystal guidance in force when the ENTRESTO NDA was submitted – and all later revisions – LCZ696 is not a co-crystal within FDA’s regulatory meaning. For example, according to the final language of FDA’s 2018 guidance, co-crystals are “[c]rystalline materials composed of two or more different molecules one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds.”³⁴ In contrast, a salt is defined as “[a]ny 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: an ionic or electrovalent crystalline compound.”³⁵ According to FDA, “[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.”³⁶ To that end, the principle that co-crystals are governed and

³² *Id.* (emphasis omitted).

³³ See, e.g., *id.* (“Novartis and the Division confirmed that though the product does not possess a drug substance-excipient co-crystal, the co-crystal guidance is being invoked to explain why the sacubitril-valsartan co-crystal is considered a drug product intermediate.”).

³⁴ Guidance for Industry – Regulatory Classification of Pharmaceutical Co-Crystals (Feb. 2018) at 4.

³⁵ *Id.*

³⁶ *Id.* at 2.

defined by non-ionic interaction is a consistent thread throughout FDA's discussion of pharmaceutical co-crystals from 2011 onwards.³⁷

While limiting the regulatory definition of co-crystals to "materials composed of two or more different molecules one of which is the API,"³⁸ FDA also clarified that a co-crystal composed of units of two or more APIs, with or without additional inactive co-formers, would be treated as a fixed-dose combination and not a new single API.³⁹ For ENTRESTO, the chemical structure of sacubitril and valsartan in the finished dosage form are defined by their ionic interactions with sodium ions resulting in the above-described complex structure. Accordingly, under FDA's definition, LCZ696 is not a co-crystal, but nonetheless remains a combination of drug substances.

At issue now is the chemical identity of the sacubitril and valsartan drug substances in the finished dosage form of the drug product prior to administration. While the physical form of a drug substance may differ from the RLD and still meet the requirements for ANDA approval, its chemical structure cannot. The chemical identity of the active ingredients in ENTRESTO is defined by specific ionic interactions comprising a specific chemical structure. Accordingly, each active ingredient in the finished dosage form of a proposed generic to ENTRESTO 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 API sameness.

b. The defined chemical structure has specific physico-chemical properties that further reflect the identity of the active ingredients in ENTRESTO

As described above, ENTRESTO neither contains a physical mixture of the free acids of sacubitril and valsartan nor does it contain a physical mixture of the individual sodium salts of sacubitril and valsartan (or other salts of sacubitril or valsartan). Instead, ENTRESTO contains a complex of sacubitril and valsartan in which the chemical structure of each active ingredient is distinct from a mixture of free acids or alternate salts of sacubitril and valsartan. The distinct

³⁷ See, e.g., *id.* (Dec. 2011, draft), at 3 ("...interact via nonionic interactions, as opposed to an ionic interaction, which would classify the crystalline soled as a salt form."). Notably, in revising a 2011 draft of the co-crystal guidance, FDA adopted in the 2013 version of the guidance new criteria for what constitutes a pharmaceutical co-crystal. In the 2011 draft guidance, FDA stated that if ΔpK_a (base-acid) < 0, a complex will generally be considered to take the form of a co-crystal, but if ΔpK_a > 3, then ionization will form a salt. *Id.* (Dec. 2011, draft). In the 2013 final guidance, FDA adopted a standard that, if $\Delta pK_a \geq 1$, "there will be substantial proton transfer resulting in ionization and potential formation of a salt as opposed to a co-crystal." *Id.* (Apr. 2013) at 3. FDA has therefore recognized that the potential to form a salt at $\Delta pK_a \geq 1$ is sufficient to distinguish between formation of a co-crystal and actual chemical modification of the API. The $\Delta pK_a \geq 1$ standard was carried through into the August 2016 revision that in turn became final in February 2018.

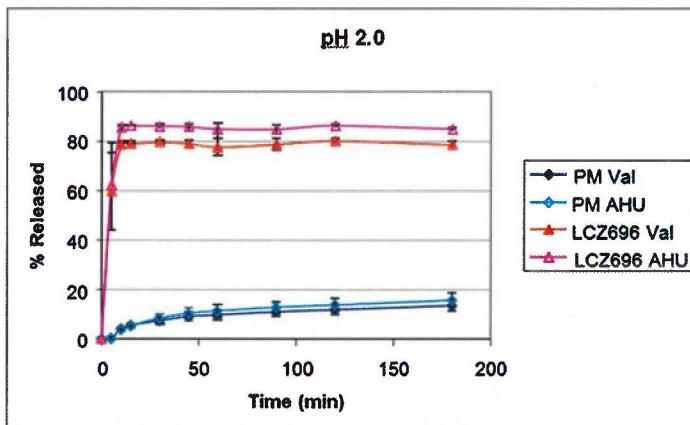
³⁸ Guidance for Industry – Regulatory Classification of Pharmaceutical Co-Crystals (Feb. 2018) at 4.

³⁹ *Id.* at 3.

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, such as sodium, potassium or other salts.

First, because both active ingredients in ENTRESTO co-exist within the same complex structure, they can only be released simultaneously at a 1:1 molar ratio. In contrast, in a typical combination product, each component is released based on its own unique solubility profile. Novartis conducted *in vitro* dissolution studies in buffer solutions of pH 2.0, 4.5, and 6.8, comparing the complex structure (LCZ696) in ENTRESTO to a physical mixture of valsartan (free acid) and sacubitril calcium salt, to demonstrate this effect. The results showed that LCZ696 exhibits faster dissolution rate and more favorable dissolution profile than the physical mixture of valsartan and sacubitril calcium in all conditions. LCZ696 also releases higher concentrations of valsartan and sacubitril at the end of three-hour experiments than the physical mixture at pH 2.0 and 4.5. See Figure 5, 6, and 7 below depicting the associated dissolution profiles.

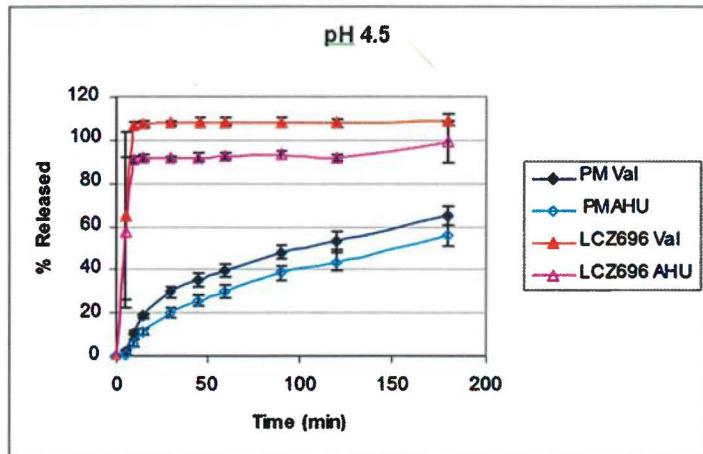
Figure 5: Dissolution profile of LCZ696 compared with a physical mixture of valsartan and sacubitril calcium (percent of drug released) at pH 2.0



PM Val = valsartan released from a physical mixture
PM AHU = sacubitril released from a physical mixture
LCZ696 Val = valsartan released from LCZ696-ABA
LCZ696 AHU = sacubitril released from LCZ696-ABA

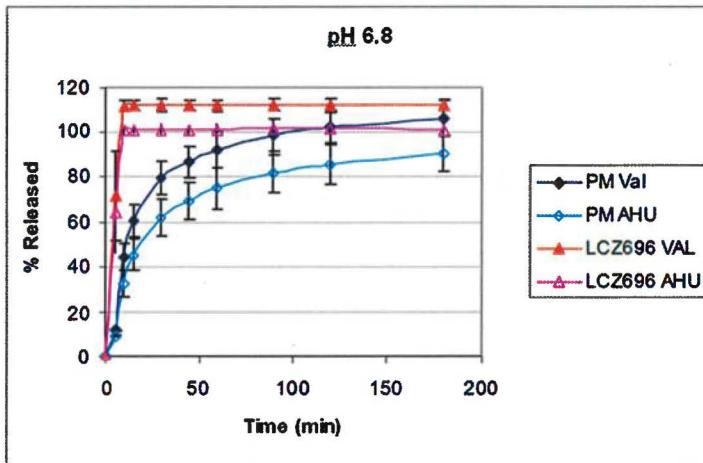
Figure 6: Dissolution profile of LCZ696 compared with a physical mixture of

valsartan and sacubitril calcium (percent of drug released) at pH 4.5



PM Val = valsartan released from a physical mixture
PM AHU = sacubitril released from a physical mixture
LCZ696 Val = valsartan released from LCZ696-ABA
LCZ696 AHU = sacubitril released from LCZ696-ABA

Figure 7: Dissolution profile of LCZ696 compared with a physical mixture of valsartan and sacubitril calcium (percent of drug released) at pH 6.8



PM Val = valsartan released from a physical mixture
PM AHU = sacubitril released from a physical mixture
LCZ696 Val = valsartan released from LCZ696-ABA
LCZ696 AHU = sacubitril released from LCZ696-ABA

Second, the active ingredients in ENTRESTO have specific solubility profiles for both sacubitril and valsartan; in particular, with valsartan showing higher solubility when delivered from LCZ696 compared to the solubility for valsartan when delivered as valsartan free acid. See Tables 1 to 3 below. Tables 1 and 2 show that valsartan had a higher solubility when it was delivered from LCZ696, and of particular note, had a very high increase in solubility at

physiological pH and in water. In water, there is an approximate 500-fold increase in valsartan solubility when delivered from LCZ696 as compared to the valsartan free acid.

Table 1: Solubility of LCZ696-ABA (at approx. 25 degrees Celsius)

Solvent	Concentration of sacubitril [mg/mL]	Concentration of valsartan [mg/mL]
0.1 N HCl	0.052	0.032
Citrate buffer, pH 3	0.38	3.8
Citrate buffer, pH 5	1.4	10.1
Phosphate buffer, pH 6.8	> 50	> 50
Water	> 100	> 100
Ethanol	> 50	> 50
Acetonitrile	1.9	1.9

Note: The solubility of LCZ696-ABA is determined by quantitation of the individual compounds using HPLC analysis.

Table 2: Solubility of valsartan (free form)

Solvent	Solubility [g/L]
0.1 N HCl	0.084
0.01 M glycine buffer, pH 3	0.104
0.067 M phosphate buffer, pH 5.2	0.64
0.067 M phosphate buffer, pH 6.0	2.82
0.067 M phosphate buffer, pH 7.4	14.4
Water	0.21
Ethanol	> 300
Acetonitrile	121-176

Table 3: Solubility of sacubitril from sacubitril calcium

Solvent	Solubility [mg/mL]
0.1 N HCl	0.17
pH 6.8 buffer	4.0
Water	1.1
Ethanol	11.7
Acetonitrile	9.2

The increase in solubility of valsartan when delivered from LCZ696 as compared to the valsartan free acid, and the dissolution profile of the LCZ696 complex, are illustrative of the distinct chemical structure of sacubitril and valsartan in the finished dosage form of ENTRESTO.

Third, the distinct chemical structure of sacubitril and valsartan in LCZ696 is evidenced *in situ*. For example, in dog PK studies, orally administered LCZ696 delivers 3 times the exposure of valsartan as do equimolar amounts of the free combination of valsartan and sacubitril.⁴⁰ Likewise, 400 mg LCZ696 (containing 206 mg valsartan) delivers exposure of valsartan equivalent to 320 mg Diovan in healthy subjects.⁴¹ Consistent with the results in healthy subjects, in heart failure patients 200 mg of LCZ696 (containing 103 mg valsartan) delivers similar exposure of valsartan compared to 160 mg Diovan. See Table 4 below. Therefore, to achieve similar valsartan exposures in humans, ~60% more valsartan administered as a physical mixture is required than that administered as LCZ696. Indeed, section 12.3 of ENTRESTO's FDA-approved label states that the "valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40mg, 80mg, and 160 mg of valsartan in other marketed tablet formulations, respectively."⁴²

⁴⁰ See Gu, J., et al., Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi), J. Clin. Pharmacol. (2010) 50: 401-414 (Tab 3).

⁴¹ See Study: LCZ696A2103 (on file at FDA).

⁴² See Package Insert 12.3 Pharmacokinetics.

Table 4: Comparative exposure of valsartan in adult heart failure patients following administration of LCZ696 or valsartan (Diovan)

		LCZ696A2117 (N = 30) ¹	LCZ696B2223 (N = 16) ¹	LCZ696B2314 (N = 311) ¹	VAL489B0105 (N = 20) ²
Valsartan	AUC _{tau} (ng*h/mL)	38807 (18129)	45700 (21800)	40912 (24975)	43540 (25897)
	C _{max,ss} (ng/mL)	6044 (2502)	6340 (2460)	4607 (2369)	6403 (3190)

Data is presented as mean (SD)

¹ Following administration of 200 mg LCZ696 twice daily² Following administration of 160 mg valsartan twice daily

These data reflect the distinct chemical structure of valsartan and sacubitril in the finished dosage form of ENTRESTO, and support the structural chemistry described above. These data provide further confirmation that the active ingredients in ENTRESTO have a defined relationship at the level of chemical structure. And, this chemical structure establishes the identity of each of the active ingredients in ENTRESTO that a proposed generic drug sponsor must match.

3. ANDA sponsors must demonstrate that their finished dosage forms contain sacubitril and valsartan complexed with Na⁺ in a 1:1:3 stoichiometry

Under the legal requirements governing the receipt and approval of drug products under section 505(j) of the FDCA, a threshold finding of “sameness” based on the chemical structure of the active ingredients must be made. For chemically synthesized, non-polymeric drug substances, the chemical structure of the active ingredients in the proposed generic drug product must be shown to be the same as the chemical structure of the active ingredients in the RLD. This requirement is separate from the requirement that a generic drug must be shown to be bioequivalent to the RLD. Thus, even if an alternative form of the active ingredients in a proposed generic to ENTRESTO were shown to be bioequivalent to ENTRESTO (based on an appropriate study), the product would still be ineligible for consideration under section 505(j) if the proposed generic were not shown to contain the identical active ingredients in the identical chemical structure as that which is described above.

A manufacturer of a generic version of ENTRESTO may be permitted to include a different polymorphic or hydrate form of the 1:1:3:2.5 sacubitril:valsartan:sodium:water complex. However, an ANDA that is based on, e.g., sacubitril and valsartan as free acids, or in an anionic state in association with a metal or cation other than Na⁺, would fail to meet the legal and regulatory standard of active ingredient sameness for generic drug products. Similarly, an ANDA based on a physical mixture of individual sodium salts (or other salts) of sacubitril and valsartan would fail to present the active ingredients in the same chemical structure as they exist in the RLD. FDA

must refrain from approving an ANDA that fails to establish API sameness based on sacubitril, valsartan and sodium, in ionic complex, in a 1:1:3 stoichiometry.

B. The Draft Guidance should be revised to be consistent with applicable legal requirements

The agency's draft bioequivalence recommendations do not establish binding requirements on the agency or on sponsors. However, to the extent that sponsors choose to follow the agency's guidance, it is imperative that the studies conducted under the guidance are adequate to meet the applicable legal requirements under section 505(j) and applicable regulations. In this instance, several changes should be made to the Draft Guidance to ensure that it conforms to the governing law on active ingredient sameness and bioequivalence.

1. Include an API equivalence recommendation to account for the chemical structure of the active ingredients in the RLD

In cases where the identity and characterization of the API presents complex scientific issues, FDA may include "API sameness" recommendations in its product-specific BE guidance documents.⁴³ This ensures that the product to be tested in the recommended bioequivalence study(ies) contains the same drug as that contained in the RLD. For products that purport to be "pharmaceutically equivalent" to an approved RLD, bioequivalence must be shown only in a product that "contain[s] identical amounts of the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moiety. . . ."⁴⁴ For ENTRESTO, where the chemical identity of the active ingredients is complex and novel (as shown in section A.2.a above, the responsible review division itself had difficulty categorizing the chemical structure of the active ingredients), an API equivalence recommendation would ensure that proposed generic drug products under section 505(j) do in fact contain sacubitril and valsartan active ingredients in an identical chemical structure to that found in ENTRESTO. Thus, for the Draft Guidance to be consistent with FDA's statutory and regulatory standards, the agency should revise the Draft Guidance 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.

⁴³ As noted in the introduction to this petition, API sameness is a prerequisite for BE and it is customary for the agency to provide recommendations on API sameness in its product-specific BE guidances when API characterization or structure is a potential issue. See, e.g., Food and Drug Administration, Draft Guidance on Glatiramer Acetate (rev. Jul. 2018); Draft Guidance on Ferric Citrate (Sept. 2015); Draft Guidance on Sevelamer Carbonate (rev. Sept. 2015); Draft Guidance on Enoxaparin Sodium (Oct. 2011).

⁴⁴ 21 CFR 314.3 (defining "bioequivalence" and "pharmaceutical equivalents").

2. *Include the primary active metabolite, sacubitrilat, as an additional analyte to be assessed for purposes of establishing BE*

The Draft Guidance for ENTRESTO recommends that applicants analyze sacubitril and valsartan in plasma, and base bioequivalence on those two active components. As mentioned above, sacubitril is an inactive prodrug that is metabolized to the active neprilysin inhibitor sacubitrilat (LBQ657) by cleavage of the ethyl ester bond by esterase catalyzed hydrolysis.⁴⁵

In demonstrating bioequivalence through an *in vivo* PK study, FDA generally recommends measurement of the parent drug released from the dosage form, rather than the metabolite. The rationale for this recommendation is that the PK profile of the parent drug is a more direct form of measurement and is generally more sensitive to changes in formulation than a metabolite. In contrast, the PK profile of a metabolite reflects the rate and extent of biochemical conversion (metabolite formation, distribution, and elimination) in addition to absorption. It is therefore a less direct means of measuring the rate and extent of absorption of the drug.⁴⁶

However, FDA's regulations provide that the active metabolite(s) should be measured in addition to the parent drug or active moiety when appropriate.⁴⁷ For example, if a metabolite is formed as a result of gut wall or other pre-systemic metabolism, and if the metabolite contributes meaningfully to the safety and/or efficacy of the drug product, FDA will recommend that both the metabolite and the parent drug be measured.⁴⁸

LBQ657 is generated pre-systemically by first pass metabolism.⁴⁹ In such cases the agency will generally recommend that the parent drug be analyzed using the confidence interval approach and that the metabolite data be used to provide supportive evidence of comparable therapeutic outcome.⁵⁰ Alternatively, FDA may require that the parent drug, the metabolite, or both, be subject

⁴⁵ See Package Insert, 12 Clinical Pharmacology.

⁴⁶ FDA Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products: General Considerations (March 2003) (BA/BE Guidance) at 18; Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Dec. 2013) (Guidance on BE for ANDAs) at 12.

⁴⁷ 21 CFR 320.24(b)(1)(i).

⁴⁸ Guidance on BE for ANDAs at 12; BA/BE Guidance at 18.

⁴⁹ See Package Insert, 12 Clinical Pharmacology. 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 CES1 was capable of hydrolysis of sacubitril to form sacubitrilat. The CES1 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.

⁵⁰ Guidance on BE for ANDAs at 12.

to statistical analysis and that one or the other, or both, meet the requirements for demonstrating bioequivalence using the confidence interval approach.⁵¹ In this case, due to the dual mechanisms of action of ENTRESTO and the nature of sacubitrilat as the therapeutic moiety for NEP inhibition, which directly contributes to the safety and efficacy of the drug product, Novartis has consistently used sacubitrilat as one of the three drug related analytes – sacubitril, sacubitrilat (LBQ657), and valsartan – for bioanalytical assessment.⁵² Similarly, ANDA sponsors should analyze these same three analytes.

Accordingly, the Draft Guidance for ENTRESTO should be revised to state that data for sacubitril, valsartan and sacubitrilat should be collected, analyzed and submitted. Individual and 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.

3. Assess the relative PK of each analyte to ensure comparability between test product and the RLD product

Because ENTRESTO relies on inhibition of neprilysin by sacubitril/LBQ657, and simultaneous AT1 receptor blockade by valsartan,⁵³ attention must be given to the relative PKs of each of the three analytes to be measured for BE purposes. The safety and effectiveness of ENTRESTO was established on the basis of a 1:1 molar ratio of sacubitril to valsartan at the level of chemical structure. Both components exist within the same complex; they are solubilized and released at the same time, with similar dissolution profiles. See Figures 5-7 and Tables 1-3 above. The release profiles from the 1:1 complex, the relative bioavailability of the APIs, and the subsequent conversion of sacubitril to the active moiety, LBQ657, support the desired combined inhibition of neprilysin and AT1 receptor blockade.⁵⁴ As noted in the FDA-approved labeling,

⁵¹ See 21 CFR 320.24(b)(1)(i); Guidance on BE for ANDAs at 12; BA/BE Guidance at 18.

⁵² See, e.g., Clinical Pharmacology and Biopharmaceutics Review(s) at p.44-45 of PDF, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ClinPharmR.pdf. Several bioequivalence and relative bioavailability studies were conducted under the development program, including the pivotal bioequivalence study for the NDA submission. In all cases, all three analytes were assessed.

⁵³ See, e.g., Package Insert, 12.1 Mechanism of Action (“The cardiovascular and renal effects of ENTRESTO in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan.”).

⁵⁴ See generally Gu, J., et al., Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi), J. Clin. Pharmacol. (2010) 50: 401-414 (Tab 3); Kobalava, Z., et al., Pharmacodynamic and pharmacokinetic profiles of sacubitril/valsartan (LCZ696) in patients with heart failure and reduced ejection fraction, Cardiovascular Therapeutics (2016) 34: 191-198 (Tab 4); Ayalasomayajula, S., et al.,

“[f]ollowing oral administration, ENTRESTO dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively.”⁵⁵ The relativity of the overlap in PK of the active constituents is recognized in the labeling, and no data exist supporting the effectiveness of a product in which the PK curves bear a different relationship to one another. Therefore, the 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.

4. Due 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

The Draft Guidance provides for a waiver request of *in vivo* testing for the 24 mg/26 mg and 49 mg/51 mg strengths based in part on “proportional similarity in the formulations of all strengths.”⁵⁶ The Draft Guidance waiver request is derived from 21 CFR 320.22(d)(2), which allows for an *in vivo* bioequivalence requirement for one or more strengths based on (1) an acceptable bioequivalence study on the designated strength, (2) acceptable *in vitro* dissolution testing of all the strengths, and (3) proportional similarity of the formulations across all strengths.⁵⁷ In FDA’s Draft Guidance for Industry on “Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA,” the term “proportionally similar” is defined as:

All active and inactive ingredients are in similar proportion between different strengths (e.g., a tablet of 50-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).⁵⁸

⁵⁵ Assessment of drug interaction potential between LCZ696, an angiotensin receptor neprilysin inhibitor, and digoxin or warfarin, Clin. Pharmacol Biopharm. (2015) 4:4 (Tab 5).

⁵⁶ Package Insert, 12.3 Pharmacokinetics.

⁵⁷ Draft Guidance (on sacubitril/valsartan), *supra* note 1.

⁵⁸ Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Dec. 2013) at 9.

⁵⁸ *Id.*

However, the 24/26 mg strength of ENTRESTO is not proportionally similar to the 49/51 mg and 97/103 mg strengths. Rather, the 24/26 mg strength tablet contains 25% active ingredient by weight, while the 49/51 mg and 97/103 mg strength tablets contain 50% active ingredient by weight. Notably, the 24/26 mg strength tablet is the same size and weight as the 49/51 mg strength tablet. Novartis formulated the 24/26 mg strength product with an increased size relative to the amount of its active ingredient in order to address concerns that the 24/26 mg strength tablet would be too small for the ENTRESTO patient population.⁵⁹ The increased size of the 24/26 mg strength tablet therefore provides an important benefit to the ENTRESTO patient population by being easier to handle for older individuals. Because of the increased size of the 24/26 mg strength tablet, and corollary lack of proportionality in formulation, Novartis conducted an *in vivo* study during the clinical development of ENTRESTO to establish bioequivalence between a 24/26 mg strength tablet with 25% active ingredient that was the same size and weight as the 49/51 mg strength tablet, and a 24/26 mg strength tablet with 50% active ingredient (*i.e.*, smaller but proportionally similar in formulation to the higher strength tablet).⁶⁰

FDA has previously spoken to the importance of generic applicants maintaining the size and shape characteristics of the RLD:

While generic formulations of [tablets and capsules] are required to be both pharmaceutically and therapeutically equivalent to [the RLD], we are concerned that differences in physical characteristics (*e.g.*, size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors.⁶¹

To that end, for purposes of “comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the Agency recommends that generic oral tablets and capsules intended to be swallowed intact should be of a similar size to the corresponding RLD.”⁶² Accordingly, Novartis believes that generic applicants should maintain the benefit of the larger size of the 24/26 mg strength tablet being easier to handle for older patients. This means the proportionality requirement for the biowaiver will not be met. Conversely, if the proportionality requirement is met, the proposed generic product will be significantly different in size.

⁵⁹ The ENTRESTO patient population has chronic heart failure (NYHA Class II-IV) and reduced ejection fraction, and the average age of the ENTRESTO patient population is higher than that of the average age of the United States population. The mean age of patients in the ENTRESTO pivotal trial, PARADIGM-HF, was 64 years. Package Insert, 14 Clinical Studies.

⁶⁰ See Clinical Pharmacology and Biopharmaceutics Review(s) at p.45 of PDF, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ClinPharmR.pdf.

⁶¹ Guidance for Industry – Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules (June 2015) at 1.

⁶² *Id.* at 4. The agency’s specific recommendations as to tablet size tolerances are listed in the guidance. *Id.* at 4 – 5.

Commissioner of Food and Drugs

April 18, 2019

Page 25

Accordingly, Novartis believes that FDA should revise the Draft Guidance to recommend an *in vivo* study to establish bioequivalence between the RLD 24/26 mg strength tablet (with 25% active ingredient) and the generic counterpart at the same dose strength.

III. CONCLUSION

For all of the reasons described above, Novartis respectfully requests that FDA grant the actions requested in this citizen petition.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

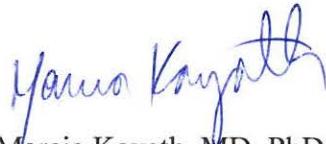
ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 15, 2016 (notice in federal register announcing availability of Draft Guidance); February 25, 2019 (most recent notice in federal register announcing new and revised product specific guidances). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None, other than my compensation as an employee of Novartis. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



Marcia Kayath, MD, PhD
Head, US Clinical Development & Medical Affairs
US Pharma
Novartis Pharmaceuticals Corporation

Enclosures