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September 12, 2022

By Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of Novartis Pharmaceuticals Corporation (Novartis), submits this petition under Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs (the Commissioner) take the actions set forth below with respect to abbreviated new drug applications (ANDAs) referencing ENTRESTO (sacubitril and valsartan) oral tablets.[1]

Novartis is the sponsor of new drug application (NDA) 207620 for ENTRESTO, which was initially approved in July 2015 to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction (HFrEF). That approval was based on the results of the PARADIGM-HF trial, which enrolled patients with heart failure and left ventricular ejection fraction (LVEF) $\leq$ 40%. In February 2021, the Food and Drug Administration (FDA or the agency) approved a supplement to NDA 207620, based largely on the results of a new clinical trial, PARAGON-HF, which enrolled patients with chronic heart failure and LVEF $\geq$ 45%. Based on the combined results of both trials, the ENTRESTO indication was expanded to include chronic heart failure patients with LVEF > 40%, including those with preserved ejection fraction (HFpEF). The labeling now states that "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."

[1] Novartis previously raised the issues discussed herein in a citizen petition dated November 30, 2021. FDA denied the previous petition for non-substantive reasons. Docket No. FDA-2021-P-1286-0014 (April 29, 2022) ("[W]e deny without comment the specific requests in the Petition regarding the approvability of ANDAs referencing Entresto."). Novartis is therefore submitting the current petition, which is substantively the same as the previous petition, to ensure that FDA carefully considers these important issues prior to approving any application submitted under section 505(j) of the FDCA that references ENTRESTO.

Following approval of the February 2021 supplement, FDA recognized 3-year exclusivity for NDA 207620 because the PARAGON-HF trial was a new clinical investigation that was essential to approval of the supplement. That exclusivity expires on February 16, 2024, and covers the revisions to the ENTRESTO labeling – including the indication statement – that arise from the PARAGON-HF trial and the use in patients with LVEF > 40%. In addition, Novartis timely listed three patents in the *Orange Book* that cover methods of using sacubitril and valsartan in heart failure patients with preserved ejection fraction: US Patent Nos. 9,517,226 (the '226 Patent), 9,937,143 (the '143 Patent), and 11,135,192 (the '192 Patent) (collectively, the HFpEF Patents). Generic applicants relying on ENTRESTO NDA 207620 as their reference listed drug (RLD) must therefore provide a patent certification or a "section viii statement" to these patents.

Based on publicly available information, at least eighteen sponsors have submitted ANDAs seeking approval of a generic sacubitril and valsartan product in reliance on ENTRESTO NDA 207620 as the RLD. Novartis timely initiated patent litigation against these ANDA applicants, and the resultant regulatory stay is due to expire on July 7, 2023 (with pediatric exclusivity). One or more of the ANDA applicants may seek approval during the 3-year exclusivity period by proposing to omit the exclusivity-protected conditions of approval derived from PARAGON-HF. These generic applicants may also seek to submit a section viii statement to the three HFpEF Patents along with a proposal to omit the labeling information claimed by these patents. In particular, one or more ANDA applicants may seek approval for an indication that omits the expanded patient population approved in February 2021 – which includes HFpEF patients – in favor of an indication statement limited to HFrEF patients.[2] For the reasons described below, FDA should refrain from approving such an ANDA product.

Congress has chosen to incentivize sponsors to invest in clinical investigations demonstrating that an approved drug is safe and effective for a new use. The FDCA implements this incentive by granting that sponsor – for a limited period – exclusive use of the labeling based on the results of such a new clinical investigation. In this case, FDA awarded ENTRESTO 3-year exclusivity because Novartis conducted a new clinical investigation (PARAGON-HF) to demonstrate that ENTRESTO is safe and effective in a wider range of patients suffering from chronic heart failure than had previously been approved. Based on the results of PARAGON-HF, FDA significantly revised the labeling for ENTRESTO to cover the entire patient population that can benefit from the drug's use and did so without reference to LVEF as a strict diagnostic criterion or fixed patient classification.

A generic applicant that seeks approval during the statutory exclusivity period cannot include the protected use in its labeling. To enable ANDA applicants to omit the protected use in this case,

[2] We note that the use in HFrEF patients is also covered by several listed patents (*e.g.*, US Patent Nos. 8,796,331 and 9,388,134). To the best of Novartis's knowledge, all ANDA applicants have submitted certifications to at least one of these patents. Accordingly, for purposes of this citizen petition, Novartis takes no position regarding the implications of a section viii statement to these patents.

FDA would have to add wording or make other changes to the existing ENTRESTO indication statement. However, such an approach is not consistent with FDA precedent and longstanding agency interpretations of the ANDA "same labeling" regulations. Under these regulations, an ANDA applicant not seeking approval for a patent- or exclusivity-protected use must start with the currently approved RLD labeling and may ***omit*** sections, or specific words and phrases, to avoid disclosing the protected use. Here, the evolution of the ENTRESTO indication statement following approval of the 2021 supplement precludes such an approach.

In addition, generic applicants cannot reference discontinued labeling, such as the now-superseded ENTRESTO indication statement describing its use in patients with "reduced ejection fraction." Moreover, an ANDA indication statement that categorizes the patient population by reference to ejection fraction would be inconsistent with the current ENTRESTO labeling, which reflects the agency's decision to no longer use LVEF as a strict diagnostic criterion to determine which patients may benefit from ENTRESTO. As the agency emphasized in promulgating the "same labeling" regulations, "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand name counterpart."[3]

For these reasons, FDA should refrain from approving an ANDA relying on ENTRESTO NDA 207620 at least until after the expiration of the 3-year exclusivity in February 2024. Upon expiration of the 3-year exclusivity period, an ANDA applicant would be required to submit a patent certification to the HFpEF Patents. For the reasons described above, an ANDA applicant cannot submit a section viii statement and labeling that proposes to omit the patented use in HFpEF patients.

In addition, the approved labeling for ENTRESTO describes a modified dosing regimen for patients who are not taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), or who were previously taking low doses of these agents. Specifically, Section 2.5 of the ENTRESTO labeling directs physicians and patients to initiate treatment with a reduced dose of sacubitril and valsartan and then to up-titrate to the target dose over a greater number of titration steps than is used for other patients. This modified dosing regimen is derived from the TITRATION study, which demonstrated that the reduced starting dose and slower titration schedule result in fewer clinically relevant adverse events for this patient group.

Novartis timely listed in the *Orange Book* US Patent No. 11,058,667 (the '667 Patent), which claims the use of the modified dosing regimen in HFrEF patients. ANDA applicants relying on ENTRESTO NDA 207620 must therefore provide a patent certification or section viii statement to this patent. Generic applicants may elect to submit a paragraph IV certification and include the modified dosing regimen in their labeling. However, one or more ANDA applicants may seek to submit a section viii statement and thereby omit the patent-protected dosing regimen for this important group of patients. In that case, FDA should refrain from approving that ANDA until the

[3] 57 FR 17949, 17962 (Apr. 28, 1992).

expiration of the ‘667 Patent because an ANDA product whose labeling does not include the modified dosing regimen for HFrEF patients would be less safe and effective than ENTRESTO for the remaining conditions of use that are not protected by the ‘667 Patent.

ACTIONS REQUESTED

Novartis requests that the Commissioner:

1. Refrain from approving any ANDA referencing NDA 207620 during the 3-year exclusivity period covering the labeling changes approved in the February 2021 supplement, including any ANDA that seeks to add language to, or otherwise revise, the existing indication statement in order to omit the exclusivity-protected use. Approving an ANDA during the exclusivity period exceeds FDA’s statutory and regulatory authority with regard to ANDA “same labeling” standards and would represent an impermissible departure from longstanding agency precedent and interpretations.

2. Refrain from approving any ANDA referencing NDA 207620 until the expiration of the HFpEF Patents if that ANDA contains a section viii statement to these patents and seeks to omit the patent-protected use in HFpEF patients. As with the 3-year exclusivity described above, FDA cannot draft an indication statement for a proposed ANDA product by deleting the use protected by the HFpEF Patents from the current ENTRESTO indication statement.

3. Refrain from approving any ANDA referencing NDA 207620 until the expiration of the ‘667 Patent if that ANDA contains a section viii statement and seeks to omit the modified dosing regimen for HFrEF patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents. Omission of this patent-protected dosing regimen would lead to an increase in clinically significant adverse events for such patients under the higher starting dose and quicker up-titration schedule described in the standard dosing regimen. Moreover, an increase in adverse events could result in diminished effectiveness if these patients are unable to tolerate the standard starting dose and titration schedule. For these reasons, an ANDA product that omits this information would be less safe and effective than ENTRESTO for the remaining conditions of use that are not protected by the ‘667 Patent.

STATEMENT OF GROUNDS

I. FACTUAL BACKGROUND

A. Heart Failure and Left Ventricular Ejection Fraction

Heart failure (HF) is a complex clinical syndrome that affects an estimated 6.2 million adults in the US, and its prevalence is increasing. Studies estimate that it will eventually affect over 8

million adults by 2030.[4] HF patients are commonly classified by left ventricular ejection fraction (LVEF), a widely used measure of heart pumping dysfunction.[5] The two primary classifications are patients with reduced ejection fraction (HFrEF) and patients with preserved ejection fraction (HFpEF).[6]

Although it is a common measure for classifying HF, LVEF has well-known limitations.[7] LVEF distribution varies with age and sex, thus challenging use of a single, precise threshold for "normal" ejection fraction.[8] Moreover, LVEF can change over time in the same patient with HF.[9] Some clinical guidelines have recognized that ejection fraction variations are most common for patients with LVEF between 40% and 49%.[10] Patients in this range have etiologies that share characteristics of both HFrEF and HFpEF, but may be in transition from higher to lower LVEF, or *vice versa*.[11]

Despite these limitations, LVEF remains "the most widely accepted marker of systolic function in clinical practice."[12]

B. FDA Approval of NDA 207620 for ENTRESTO

FDA first approved ENTRESTO (sacubitril and valsartan) on July 7, 2015. At that time, ENTRESTO was indicated to "reduce the risk of cardiovascular death and hospitalization for heart

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[4] S. Virani, *et al.*, *Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association*, CIRCULATION 2020 141:e139, e509 *available at* https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000000757.

[5] M. Rigolli, *et al.*, *Heart failure with preserved ejection fraction*, J. GERIATR. CARDIOL. 2013 Dec; 10(4): 369, 370 (Tab A).

[6] *Id.*

[7] *See* C. Lam, *et al.*, *Classification of Heart Failure According to Ejection Fraction*, J. AM. COLL. CARDIOL. 2021 Jun; 77(25):3217, 3222 (Tab B).

[8] Lam at 3219; *see also* R.M. Lang, *et al.*, *Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging*, J. AM. SOC. ECHOCARDIOGR. 2015;28:1, 7 (describing the normal LVEF range as 54-74 in women and 52-72 in men) (Tab C).

[9] Lam at 3222.

[10] *See* B. Bozkurt, *et al.*, *Universal definition and classification of heart failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure*, J. OF CARDIAC FAIL. (2021) 27(4):387, 392 (Tab D)

[11] *See id.* at 395.

[12] Lam at 3222.

failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction."[13] The indication statement also noted that "ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB."[14] Approval was based on the PARADIGM-HF clinical trial demonstrating safety and effectiveness of ENTRESTO for treating chronic heart failure with reduced ejection fraction.[15] The clinical studies section of the labeling describes the PARADIGM-HF patient population as including patients with LVEF $\leq 40\%$.[16]

In 2019, FDA approved an efficacy supplement for use of ENTRESTO in pediatric patients and made corresponding changes to the approved labeling based on results of the PANORAMA-HF study in pediatric patients.[17] The indication statement was updated to add that 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."[18] Weight-based dosing instructions were also added for pediatric patients, along with dose reductions for pediatric patients experiencing severe renal impairment or hepatic impairment. These labeling changes are protected by 3-year exclusivity that will expire in April 2023, including pediatric exclusivity.[19]

C. Approval of ENTRESTO sNDA in February 2021 for an Expanded Indication

In April 2020, Novartis submitted an sNDA seeking to expand the approved patient population, based on the results of the PARAGON-HF study. That study was a phase 3, randomized, double-blind, double-dummy, active-controlled trial comparing sacubitril/valsartan to valsartan alone in patients with symptomatic NYHA class II-IV heart failure. The study enrolled patients with LVEF $\geq 45\%$, including patients with preserved ejection fraction.[20] The primary efficacy endpoint was a composite of total hospitalization for heart failure (HHF) (*i.e.*, first hospitalization and recurrent hospitalizations) and cardiovascular death. The study narrowly missed statistical significance with

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[13] ENTRESTO Prescribing Information, NDA 207620 (Jul. 7, 2015), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf.

[14] *Id.*

[15] *Id.*

[16] *Id.*

[17] ENTRESTO Prescribing Information, NDA 207620 (Oct. 1, 2019), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s013lbl.pdf.

[18] *Id.*

[19] Because the 3-year exclusivity covering the pediatric use expires prior to the regulatory stay, Novartis takes no position in this petition regarding an ANDA applicant's ability to omit the pediatric information covered by this exclusivity.

[20] ENTRESTO Prescribing Information, NDA 207620 (Feb. 16, 2021) (ENTRESTO 2021 PI) at Section 14.1, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207620s018lbl.pdf.

respect to the primary endpoint; however, other supportive efficacy analyses suggested a beneficial treatment effect, particularly in patients with LVEF below normal. The Division of Cardiology and Nephrology (the Division) concluded that PARAGON-HF supported an "expansion" of the prior indication statement, in part based on the positive results in the overall patient population in PARADIGM-HF and the strength of data in the subgroup of patients with LVEF below the median in PARAGON-HF.[21] It is estimated that the resultant expansion of the indication statement "has the potential to prevent or postpone up to 180,000 worsening HF events." [22]

In February 2021, FDA approved the ENTRESTO sNDA. In doing so, the agency made several changes to the approved labeling to incorporate information derived from the PARAGON-HF study. First, the agency revised the Clinical Studies section to include a description of PARAGON-HF clinical trial data. The agency also added a figure to the approved labeling to present combined data from both PARADIGM-HF and PARAGON-HF regarding the treatment effect for the composite endpoint of time to first HF hospitalization or cardiovascular death for patients with an LVEF at screening between 15% and 75%.[23] This figure illustrates that patients with LVEF below normal experienced greater cardiovascular risk reduction following treatment with ENTRESTO.

The Adverse Reactions and Pharmacodynamics sections were also revised to include laboratory abnormalities observed during the PARAGON-HF study, as well as data from the PARAGON-HF and PARAMOUNT studies detailing decreases in NT-proBNP.[24] Additionally, the Warnings and Precautions section removed specific references to the PARADIGM-HF trial from the hypotension, impaired renal function, and hyperkalemia subsections.[25]

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[21] *See* NDA 207620/S-018, Clinical/Statistical Review (Feb. 16, 2021) (2021 Clinical Review) at 10-11, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/207620Orig1s018.pdf ("Subgroup analyses of the PARAGON-HF trial for the adjudicated primary efficacy endpoint showed that subjects with an LVEF below the median (LVEF 57%) appeared to derive benefit….The apparent benefit in subjects with reduced LVEF was consistent with the evidence from the PARADIGM-HF trial.")

[22] M. Vaduganathan, *et al*., *Potential Implications of Expanded US Food and Drug Administration Labeling for Sacubitril/Valsartan in the US*, JAMA CARDIOL. (Sept. 15, 2021) at E8 (Tab E).

[23] ENTRESTO 2021 PI at Figure 7.

[24] *See id.* at Sections 6 and 12.2. PARAMOUNT was a phase 2, double-blind, randomized, active-controlled study in HFpEF patients comparing the effect of sacubitril/valsartan to valsartan alone on changes in NT-proBNP and HF symptoms/signs. Novartis Pharmaceuticals, Cardiovascular and Renal Drugs Advisory Committee Briefing Document - Entresto for Chronic Heart Failure and Preserved Ejection Fraction at 25, *available at* https://www.fda.gov/media/144379/download.

[25] ENTRESTO 2021 PI at Section 5. Additional, minor changes to other labeling sections include editorial changes to the modified dosing regimen for patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents, and to the dose reductions for patients with severe renal and hepatic impairment.

Most notably, FDA revised the indication statement to characterize the expanded use of ENTRESTO. The previously approved use in adult patients with reduced ejection fraction was broadened to include all adult patients with chronic heart failure. The agency made significant changes to the indication statement to describe the combined patient populations as a unified indication, as the following mark-up shows (additions shown in bold underline; deletions shown with strikethrough):

> Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure ~~(NYHA Class II-IV) and reduced ejection fraction~~.
>
> ~~Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.~~
>
> **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.**

FDA awarded 3-year exclusivity upon approval of the supplement, recognizing that the PARAGON-HF study conducted by Novartis was a new clinical investigation essential to approval of the sNDA. That exclusivity will expire on February 16, 2024 and is listed in the *Orange Book* with the following exclusivity code "M-82: LABELING REVISIONS RELATED TO CLINICAL STUDIES."[26]

Following approval of the February 2021 supplement, Novartis timely listed the '226, '143, and '192 Patents, which expire on August 22, 2033. These patents are listed in the *Orange Book* with Use Code U-3084: "TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION."[27]

D. The Patent-Protected Modified Dosing Regimen

ENTRESTO is administered on a carefully designed titration schedule. The recommended starting dose for ENTRESTO is 49/51 mg (sacubitril/valsartan) twice daily. After 2 to 4 weeks, providers are instructed to double the dose of ENTRESTO to the target maintenance dose of 97/103 mg

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[26] Electronic *Orange Book*, Patent and Exclusivity Listing for NDA 207620, *available at* https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=207620&Appl_type=N.

[27] *Id.*

(sacubitril/valsartan), as tolerated by the patient.[28] Pediatric patients are dosed by weight and are instructed to follow a three-stage up-titration schedule.[29] However, the labeling provides a modified dosing regimen for patients not taking an ACE inhibitor or an ARB, or who were previously taking low doses of these agents. The modified dosing regimen for this patient population was informed by the TITRATION study, which assessed the safety and tolerability of initiating sacubitril/valsartan in heart failure patients using two different dose titration regimens.[30]

The primary tolerability assessment in TITRATION was the number and proportion of patients who experienced pre-specified adverse events, such as hypotension, renal dysfunction, and hyperkalemia.[31] The study design included a short, open-label period (5 days) during which all enrolled patients initiated sacubitril/valsartan at a dose of 24/26 mg twice daily. The patient population included a "high dose" group of patients who had previously received the equivalent of > 160 mg of valsartan or > 10 mg of enalapril daily, and a "low dose" group who had previously received the equivalent of ≤ 160 mg of valsartan or ≤ 10 mg of enalapril, or no ACE inhibitors or ARBs at all.[32] Patients were then randomized into two groups, in which one group was titrated up to the target dose of 97/103 mg sacubitril/valsartan on a 3-week "condensed" titration regimen and the other group was titrated up to the target dose of 97/103 mg sacubitril/valsartan on a 6-week "conservative" regimen to determine whether the duration of the titration regimen affected the tolerability of sacubitril/valsartan.[33]

FDA concluded that the study provided critical information that was necessary to the safe and effective use of the product:

> The results of the phase 2 dose regimen study (TITRATION) suggests that patients who were previously on low dose of [ACE inhibitors] and ARBs might benefit from a slow up-titration regimen (a 6-week regimen) rather than a fast up-titration regimen (a 3-week regimen) to increase tolerability and reduce the risk of adverse

[28] ENTRESTO 2021 PI at Section 2.2.

[29] *Id*. at 2.3.

[30] NDA 207620, Clinical Review (May 15, 2015) (2015 Clinical Review) at 69, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000MedR.pdf; *see also* ClinicalTrials.gov Study Record Detail *available at* https://clinicaltrials.gov/ct2/show/NCT01922089.

[31] M. Senni, *et al.*, *Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens*, EUR. J. HEART FAIL. 2016 Sep;18(9):1193, 1195 (Tab F).

[32] 2015 Clinical Review at 69.

[33] *Id*.

> events such as hypotension, hyperkalemia and renal impairment. We agree with the proposed titration strategy from a safety perspective.[34]

The results of the TITRATION study were submitted with the original ENTRESTO NDA, and the modified dosing regimen has been included in the approved labeling since the time of initial approval in July 2015.[35] According to the modified dosing regimen, adult patients not taking an ACE inhibitor or an ARB, or who were previously taking low doses of these agents, are instructed to start at half the recommended starting dose, *i.e.*, a dose of 24/26 mg sacubitril/valsartan, and to slowly titrate to the target dose over two additional stages.[36] Similarly, Section 2.5 states that pediatric patients not taking an ACE inhibitor or an ARB, or who were previously taking low doses of these agents, should be started at half the recommended starting dose (which is dependent on weight), with increases in dose every two weeks according to the standard pediatric dosing regimen.[37]

Novartis is the owner of US Patent No. 11,058,667 (the '667 Patent), which issued on July 13, 2021. The '667 Patent claims the modified dosing regimen included in Section 2.5 with regard to those patients with HFrEF. Novartis timely submitted information for listing the '667 Patent in the *Orange Book*. This patent expires on May 9, 2036 and is currently listed in the *Orange Book* with Use Code U-3170, which encompasses the modified dosing regimen described in Section 2.5 of the currently approved labeling:

> TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE.[38]

[34] *Id.* at 80.

[35] The modified dosing regimen in Section 2.5 was revised in 2019 to incorporate instructions for pediatric patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents, and in 2021 to include minor editorial changes.

[36] ENTRESTO 2021 PI at Section 2.5. ENTRESTO is administered to pediatric patients on a weight-based dosing schedule over the course of three stages. *Id.* at Section 2.3.

[37] *Id.* at Section 2.5.

[38] Electronic *Orange Book*, Patent and Exclusivity Listing for NDA 207620. The '667 Patent claims the modified dosing regimen with regard to adult HFrEF patients and a subset of pediatric HFrEF patients.

E. ANDA Applications Relying on ENTRESTO as the Reference Listed Drug

According to publicly available information, at least 18 ANDAs have been submitted to FDA for sacubitril and valsartan products relying on ENTRESTO as the RLD.[39] In October 2019, Novartis timely filed lawsuits against these ANDA filers for patent infringement, thereby triggering a regulatory stay on FDA's authority to grant final approval to these ANDAs. That stay will expire in July 2023 (with pediatric exclusivity). Lawsuits are currently pending, and a trial in the US District Court for the District of Delaware involving two *Orange Book* listed patents has been scheduled to start on September 12, 2022. In 2021 and 2022, Novartis filed additional lawsuits against certain ANDA filers that provided notice to Novartis regarding paragraph IV certifications to the '226, '143, '192, and '667 Patents, including 11 lawsuits against ANDA filers regarding the '667 Patent, two of which are currently stayed. Trial involving the '667 Patent is scheduled to commence trial in the US District Court for the District of Delaware on February 12, 2024.

II. LEGAL BACKGROUND

A. Patent Listing and Use Codes for NDAs

An NDA applicant must submit information for each patent that claims the drug approved in its application, or a method of using such drug, and with respect to which a claim of patent infringement could reasonably be asserted against an unlicensed person engaged in the manufacture, use, or sale of the drug.[40] For patents that claim an approved method of use, the NDA holder must provide a 250-character description, *i.e.*, a Use Code, that describes the approved indication or condition of use that is covered by the patent.[41]

B. 3-Year Exclusivity

FDA may award a 3-year period of exclusivity to an original NDA for a previously approved drug, if that NDA contains "new clinical investigations" that were "essential to approval," and were "conducted for or sponsored by" the applicant.[42] During the exclusivity period, FDA will not grant final approval to an ANDA with the same "conditions of approval" as the approved drug.[43] Similarly, FDA will also award a period of 3-year exclusivity for sNDAs that contain "new clinical investigations … essential to the approval of the supplement and conducted or sponsored by the

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[39] FDA, Paragraph IV Patent Certifications (Sept. 5, 2022), *available at* https://www.fda.gov/media/133240/download.

[40] 21 USC 355(b)(1)(A)(viii).

[41] 21 CFR 314.53(b)(1).

[42] *See* 21 USC 355(c)(3)(E)(iii); 21 CFR 314.108(b)(4).

[43] 21 CFR 314.108(b)(4)(iv).

person submitting the supplement."[44] In the case of a supplement containing a new clinical investigation, the statute provides that FDA is precluded from approving an ANDA "for a change approved in the supplement."[45] Notwithstanding the different statutory language, FDA has interpreted the phrase "change approved in the supplement" to be analogous to "conditions of approval" as used in the provision for original NDAs.

The term "conditions of approval" is not defined by statute or regulation. Nevertheless, FDA has stated that the scope of 3-year exclusivity is related to the scope of the underlying new clinical investigation that was essential to the application's approval.[46]

C. ANDA Approval Standards

An ANDA applicant may rely for approval on the agency's previous findings of safety and effectiveness for an RLD approved in an NDA, as those findings are reflected in the RLD's approved labeling.[47] To rely on these findings, an ANDA applicant must demonstrate that its proposed product is (1) the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, and strength, and (2) bioequivalent to the RLD.[48] An ANDA product must also have the same labeling as the RLD, with limited exceptions noted below.

In exchange for the ability to rely on the RLD approval, ANDA applicants must submit an appropriate patent certification or statement for each patent timely listed in the *Orange Book* with the RLD product.[49] An ANDA applicant seeking approval for a use covered by a listed patent may challenge that patent by submitting a paragraph IV certification. Alternatively, an ANDA applicant may submit a section viii statement indicating that the applicant does not seek approval for the conditions of use claimed by the patent.[50] If the ANDA applicant submits a section viii statement, it must omit from its labeling the use covered by the patent, as described in the Use Code provided by the RLD sponsor.[51]

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[44] 21 USC 355(c)(3)(E)(iv).

[45] *Id.*

[46] *See, e.g.*, FDA Petition Response regarding Trintellix (vortioxetine), Docket No. FDA-2019-P-0837 (Jul. 18, 2019) at 11, *available at* https://www.regulations.gov/document/FDA-2019-P-0837-0026.

[47] *See* 21 USC 355(j)(2)(A)(v).

[48] *See* 21 USC 355(j)(2)(A); 21 CFR 314.92(a)(1).

[49] 21 USC 355(b)(2)(B); 355(j)(2)(A)(viii).

[50] 21 USC 355(j)(2)(A)(viii).

[51] *See* 68 FR 36676, 36682 (Jun. 18, 2003) ("In determining whether an ANDA applicant can 'carve out' the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.").

D. ANDA "Same Labeling" Requirements

Generally, the FDCA requires that an ANDA have the same labeling as the RLD. The statute provides that ANDA labeling may differ from the RLD labeling only if those differences are due to a suitability petition or the fact that the products are manufactured and distributed by different companies.[52] In turn, FDA regulations provide that labeling differences may include "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act" so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[53]

III. FDA SHOULD REFRAIN FROM APPROVING ANY ANDA THAT OMITS THE 2021 LABELING REVISIONS PROTECTED BY 3-YEAR EXCLUSIVITY AND THE HFpEF PATENTS.

For ENTRESTO, the new use in an expanded population of all patients with chronic heart failure – including patients with HFpEF – is protected by both 3-year exclusivity and the HFpEF Patents. As a result, the only condition of use for which ANDA applicants could seek approval during the 3-year period is in a HFrEF patient population.[54] In the unique circumstances of this case, however, the evolution of the ENTRESTO indication statement precludes an ANDA applicant from deriving an indication limited to HFrEF patients by simply omitting the protected use. Longstanding FDA precedent also makes clear that FDA may not revise or alter the wording of the existing indication statement to draft novel ANDA labeling that does not disclose ENTRESTO's protected use.

A. The Revised Indication Statement and Other Labeling Added in February 2021 are Protected by 3-Year Exclusivity.

FDA recognized 3-year exclusivity following approval of a supplement to ENTRESTO NDA 207620 on February 16, 2021, based largely on the results of PARAGON-HF. Thus, FDA is prohibited from approving an ANDA until February 16, 2024 for the conditions of approval arising from the 2021 supplement. The scope of this 3-year exclusivity – *i.e.*, the conditions of approval that are protected by the exclusivity – includes all of the labeling changes arising from the PARAGON-HF study, which provided essential new information regarding the safety and efficacy of ENTRESTO in treating an expanded set of patients. The changes to the ENTRESTO indication statement, in particular, arise directly from the PARAGON-HF trial.

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[52] 21 USC 355(j)(2)(A)(v).

[53] 21 CFR 314.94(a)(8)(iv); 21 CFR 314.127(a)(7).

[54] Because the conditions of approval protected by the 3-year exclusivity overlap with the use claimed by the HFpEF patents, an ANDA applicant seeking approval during the 3-year exclusivity period would also have to submit a section viii statement with regard to these patents.

Although the PARAGON-HF trial narrowly missed statistical significance with respect to its primary endpoint, ENTRESTO was shown to reduce the rate of the primary composite endpoint of total (first and recurrent) HF hospitalizations and cardiovascular death by 13% relative to the active comparator. Importantly, the agency considered PARAGON-HF to provide evidence of efficacy in a novel patient population that was not studied in the PARADIGM-HF trial, which had included patients with LVEF ≤ 40%.[55]

As a result, FDA's conclusions regarding the findings of PARAGON-HF led the agency to revise the indication statement for adults as follows (additions shown in bold underline; deletions shown with strikethrough):

> Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure ~~(NYHA Class II-IV) and reduced ejection fraction~~.
>
> ~~Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.~~
>
> **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.**

The key revision was to expand the indication beyond the population of adult patients evaluated in PARADIGM-HF – *i.e.*, those with chronic heart failure and reduced ejection fraction – to encompass those patients with LVEF > 40%, including patients with preserved ejection fraction.[56] In doing so, the agency deleted the reference to "reduced ejection fraction" used to define the previously approved patient population. Moreover, the agency elected not to include a term such as "preserved ejection fraction" to define the newly approved population studied in PARAGON-HF; nor did the agency use numerical ranges of LVEF (*e.g.*, ≤ 40% or ≥ 45%) to describe the studied populations. Instead, the agency added two statements emphasizing the importance of taking a patient's LVEF into consideration: "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal," and "LVEF is a variable measure, so use clinical judgment in deciding whom to treat."

[55] 2021 Clinical Review at 11, 14.

[56] In addition, the agency made two relatively minor changes to the indication statement. First, the reference to use in place of an ACE inhibitor or an ARB was deleted from the indication statement and moved to Sections 4 and 7. Second, the agency deleted the reference to "(NYHA Class II-IV)" classification of HF patients.

These additions highlight the agency's recognition of the similarities between the clinical presentations of HFrEF and HFpEF. In its review of the 2021 sNDA, the agency summarized the treatment effect of other heart failure therapies in patient groups classified by LVEF and commented that HF patients with LVEF in the 40-55% range "tend to derive benefit from therapies that are efficacious in patients with HFrEF with LVEF < 40%."[57]

In addition to the indication statement, the approved labeling was revised to include the following figure, which analyzes data from both PARADIGM-HF and PARAGON-HF to show that patients with LVEF "below normal" experienced greater risk reduction when treated with ENTRESTO.[58]

Figure 7: Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF

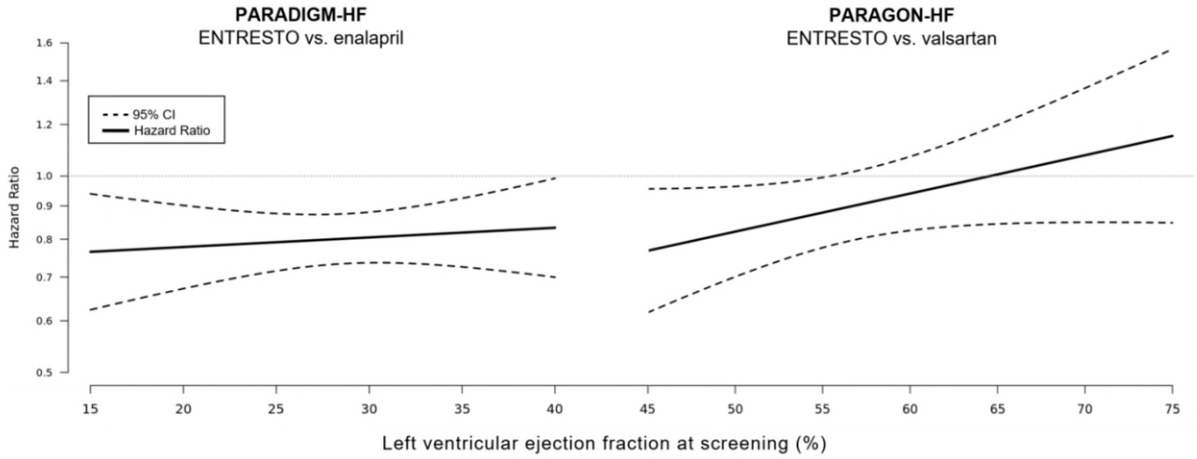

Figure 7 allows physicians and patients to understand the treatment effect of ENTRESTO across a range of LVEF values and to make an informed treatment decision for an individual patient.

Other key labeling changes include the addition of information in the Clinical Studies section to describe the PARAGON-HF trial and its results.[59] The agency also revised the following sections of the ENTRESTO labeling:

- Specific references to the PARADIGM-HF data in Section 5.3, Hypotension, Section 5.4, Impaired Renal Function, and Section 5.5, Hyperkalemia were removed;[60] and Section

[57] 2021 Clinical Review at 55.

[58] *See id.* at 53 ("Greater benefit of Entresto observed in patients with lower LVEF in HFpEF is likely a credible finding given … [the] known treatment effect of Entresto in an adjacent patient population i.e.; patients with HFrEF with LVEF < 40%.")

[59] ENTRESTO 2021 PI at Section 14.

[60] *Id.* at Section 5.

12.2, Pharmacodynamics, was revised to add data from PARAGON-HF on the decrease in NT-proBNP in the studied population.[61]

B. The Revised Indication Statement and Other Labeling Added in February 2021 are also Claimed by the HFpEF Patents.

The HFpEF Patents claim the labeling information added in 2021 that describes the HFpEF subset of the approved patient population. Accordingly, the HFpEF Patents were timely listed by Novartis in the *Orange Book* with Use Code U-3084: "TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION."[62] Specifically, the labeling describing the clinical study results from PARAGON-HF and the expanded indication statement directed to patients with HFpEF are covered by the method of use claimed by the HFpEF Patents, as described in the published Use Code.

C. FDA Should Refrain from Approving an ANDA with Labeling that Adds Language to, or otherwise Revises, the Current Indication Statement.

An ANDA applicant seeking approval of a generic sacubitril and valsartan product during the 3-year exclusivity period must omit the labeling information that is protected by that exclusivity and the HFpEF Patents. All of the labeling information informed by the PARAGON-HF study is within the scope of ENTRESTO's 3-year exclusivity, and an ANDA applicant must therefore omit from its labeling all information describing any of the protected conditions of approval. Similarly, the HFpEF Patents cover the approved use in adult patients with heart failure and preserved ejection fraction. As a result, an ANDA applicant that proposes to submit a section viii statement to the HFpEF Patents must also ensure that its labeling does not disclose the use described by the Use Code listed with the HFpEF Patents.[63]

FDA's authority to approve an ANDA that omits protected uses from its labeling is limited by the statutory and regulatory rules governing the labeling of drug products submitted in ANDAs. The FDCA permits ANDA applicants to seek approval for fewer than all conditions of use of the approved RLD. However, in such situations, an ANDA applicant must nevertheless meet the regulatory "same labeling" requirements. In pertinent part, an ANDA product must have the same labeling as the RLD "except for changes required … because the new drug and the listed drug are produced or distributed by different manufacturers."[64] By regulation, FDA has established the following list of permissible differences:

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[61] *Id*. at Section 12.2.

[62] Electronic *Orange Book*, Patent and Exclusivity Listing for NDA 207620.

[63] At least one ANDA applicant has provided notice to Novartis regarding paragraph IV certifications to the HFpEF Patents.

[64] 21 USC 355(j)(2)(A)(v).

> Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in the expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or ***omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F)*** of the Federal Food, Drug, and Cosmetic Act.[65]

Changes to the labeling not captured in this list cannot be submitted in an ANDA, and sponsors of proposed ANDA products may instead be required to submit a 505(b)(2) NDA.[66]

In promulgating this rule, the agency emphasized that the exceptions are limited.[67] In particular, FDA expressly rejected stakeholder comments requesting that the agency "permit ANDA applicants to deviate from the labeling for the reference listed drug to add" safety-related information.[68] In so doing, the agency emphasized that "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart."[69]

This approach is consistent with the agency's acknowledgment that the statute and regulations require an ANDA applicant to demonstrate that its proposed labeling is the same as the ***current*** labeling for the RLD product. As the agency described in a recent petition response regarding the omission of information protected by 3-year exclusivity for the product Fanapt (iloperidone):

> [I]n considering whether a proposed ANDA can be approved in light of this exclusivity, FDA must start with the currently approved labeling, determine which labeled information was derived from the new clinical study … and is therefore protected, and assess whether an ANDA ***with this information deleted*** pursuant to the FD&C Act and regulations remains safe and effective for the remaining, non-protected conditions of use. ***Statements that appeared in earlier versions of the drug's labeling but no longer appear in the currently approved labeling have no relevance to this inquiry***.[70]

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[65] 21 CFR 314.94(a)(8)(iv) (emphases added).

[66] *Draft Guidance for Industry; Determining Whether to Submit an ANDA or a 505(b)(2) Application* at 13 (May 2019), *available at* https://www.fda.gov/media/124848/download.

[67] *See* 54 FR 28872, 28884 (Jul. 10, 1989) ("FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited.").

[68] 57 FR 17949, 17961 (Apr. 28, 1992).

[69] *Id.*

[70] FDA Petition Response regarding Fanapt (iloperidone), Docket No. FDA-2016-P-2654 (Nov. 28, 2016) (Fanapt Petition Response) at 9 (internal footnote omitted) (emphases added), *available at*

In addition to the omission of labeling sections or the "selective deletion" of words or phrases, FDA has permitted ANDA labeling to include so-called "*de minimis*" changes, *i.e.*, "minor attendant changes to ensure that the language of the labeling reads properly."[71] For example, the agency has substituted references to a protected indication with the phrase "another indication."[72]

However, the governing regulations and FDA's own longstanding interpretation of those regulations both make clear that the agency is not permitted to make additions to the labeling of a proposed ANDA product or to otherwise re-write an indication statement or other protected sections of the labeling.[73] Such an approach would lead to inconsistent labeling between generic drugs and their branded RLDs, which the agency recognized could lead to confusion and uncertainty regarding the safety and efficacy of the generic products.[74] Indeed, when faced with a similar situation involving the drug product Precedex (dexmedetomidine hydrochloride), FDA sought public stakeholder input to determine whether it was "acceptable to add new words to the

https://www.regulations.gov/document/FDA-2016-P-2654-0008. FDA's insistence on use of the current RLD labeling also reflects the agency's longstanding position that an ANDA applicant can rely on the findings of safety and effectiveness of an RLD, only to the extent that those findings are described in the RLD labeling.

[71] FDA Petition Response regarding Lyrica (pregabalin), Docket No. FDA-2010-P-0087 (Aug. 3, 2010) (Lyrica Petition Response) at 9, *available at* https://www.regulations.gov/document/FDA-2010-P-0087-0004.

[72] FDA Petition Response regarding Treanda (bendamustine hydrochloride), Docket No. FDA-2015-P-3980 (Mar. 24, 2016) (Treanda Petition Response) at 16 (noting that "the term 'NHL' will be removed and replaced with the generic descriptor, 'another indication'" to avoid disclosing the Non-Hodgkin's Lymphoma indication protected by orphan exclusivity), *available at* https://www.regulations.gov/document/FDA-2015-P-3980-0021.

[73] Notably, Congress expressly provided FDA with additional authority to add language to an ANDA product's labeling when omitting ***a protected pediatric use***. *See* 21 USC 355a(o)(2). In that limited situation, FDA is authorized to add a disclaimer statement to the ANDA labeling to indicate that the RLD product is also approved for a pediatric use that is protected by patent or exclusivity. *Id*. at 355a(o)(2)(A). Additionally, the agency may include statements regarding any relevant contraindications or other safety information "necessary to assure safe use." *Id*. at 355a(o)(2)(B). The need for such a provision – and the absence of a similar provision for non-pediatric uses – indicates that FDA does not otherwise have authority to add wording to an ANDA product's labeling in this fashion to ensure the omission of protected uses.

[74] *See* note 67 above.

approved indication to limit the indication to exclude" the use protected by a listed method of use patent.[75] Ultimately, FDA decided the Precedex matter without addressing this issue.[76]

In the case of ENTRESTO, the use in heart failure patients with reduced ejection fraction is not protected by the HFpEF Patents and the 3-year exclusivity. However, this use is no longer expressly described in the current indication statement, and there is therefore no permissible way for an ANDA applicant to omit the protected use from the current indication statement to describe only the use in patients with reduced ejection fraction:

> Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in 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.

Selective deletions to remove the wording added to the indication statement upon approval of the February 2021 supplement would result in an indication – "Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure" – that is impermissibly broader than the reduced ejection fraction use.

Similarly, any changes to revise the ENTRESTO indication statement to exclude the use protected by exclusivity and the HFpEF Patents would be more than mere *de minimis* changes. FDA has repeatedly characterized *de minimis* changes as "minor attendant changes to ensure that the language of the labeling reads properly."[77] Adding wording to the labeling of a proposed sacubitril and valsartan ANDA product's indication statement would impermissibly exceed the type of minor stylistic edits previously described by the agency. For example, adding language to remove patients with "preserved ejection fraction" or to limit the patient population to patients with "reduced ejection fraction" would be a substantive change, not permitted by FDA regulations or precedent. If FDA is considering allowing an ANDA applicant referencing ENTRESTO to remove the protected PARAGON-HF information by adding new language to the indication, the agency must at the very least seek public comment on the issue, consistent with FDA's treatment of Precedex.

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[75] FDA Dear Applicant Letter regarding Precedex (dexmedetomidine hydrochloride), Docket No. FDA-2014-N-0087-0001 (Jan. 15, 2014) at 2, *available at* https://www.regulations.gov/document/FDA-2014-N-0087-0001.

[76] *See* FDA Dear Applicant Letter regarding Precedex (dexmedetomidine hydrochloride), Docket No. FDA-2014-N-0087-0025 (Aug. 18, 2014) at 1, *available at* https://www.regulations.gov/document/FDA-2014-N-0087-0025.

[77] Lyrica Petition Response at 9; Treanda Petition Response at 15.

D. FDA should Refrain from Approving a Generic Sacubitril and Valsartan Product Proposing an Indication Statement that has been Discontinued for ENTRESTO.

ANDA applicants may seek to use the superseded ENTRESTO indication statement as it existed prior to approval of the ENTRESTO sNDA in February 2021 in order to describe a use in patients with reduced ejection fraction, *i.e.*, one that is not protected by the HFpEF Patents and the 3-year exclusivity. Such an approach is not permissible. ANDA applicants are not permitted to rely on discontinued labeling, and FDA may not approve an ANDA with such labeling.

1. The statute and regulations do not authorize an ANDA applicant to reference discontinued labeling for ENTRESTO.

In 2000, FDA issued a draft guidance document proposing to allow generic sponsors to copy "discontinued labeling" if the agency determined that the labeling had not been discontinued for safety or effectiveness reasons.[78] However, FDA withdrew the draft guidance after receiving comments questioning its legality due to its inconsistency with the statute.[79]

The FDCA and FDA regulations are clear that the agency cannot approve an ANDA proposing to substitute discontinued RLD labeling for the protected use in the currently approved RLD labeling. As noted above, FDA regulations and precedent require that the ANDA applicant compare its proposed labeling to "currently approved" labeling for the listed drug.[80] A key element of the regulations is that FDA may allow *limited* omissions in ANDA labeling. Even if FDA interprets omissions broadly to include *de minimis* changes, such changes are distinct from the reintroduction of superseded information from an RLD's discontinued labeling. Allowing generic applicants to rely on the discontinued labeling for ENTRESTO would exceed FDA's legal authority and constitute an unjustified reversal of agency precedent.

2. The evolution of the ENTRESTO indication statement differs from situations in which FDA has effectively permitted an ANDA sponsor to return to a previously approved indication statement.

FDA determined that it would permit certain labeling changes involving the drug Velcade (bortezomib) by allowing the generic applicants to use a previously approved, but superseded,

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[78] *See Draft Guidance for Industry, Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications* (Oct. 2000) (Tab G).

[79] 78 FR 48175 (Aug. 7, 2013) (noting that "[t]he guidances are being withdrawn because they are out of date, thus of little use to the pharmaceutical industry").

[80] 21 CFR 314.94(a)(8)(v).

indication statement.[81] In that case, Velcade was initially approved for "treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy" (*i.e.*, second-line mantle cell lymphoma). Subsequently, FDA approved a supplement to the Velcade NDA containing data supporting the product's use in first-line mantle cell lymphoma. Upon approval of this supplement, the agency modified the indication statement to read simply "for the treatment of patients with mantle cell lymphoma," without any specific reference to first-line or second-line treatment.

ANDA applicants sought approval to exclude the protected first-line use by reverting back to the previous, discontinued indication statement describing second-line use. Velcade's sponsor submitted a citizen petition to FDA requesting that the agency not approve the proposed ANDA labeling. FDA denied the petition, based on its conclusion that ANDAs could be labeled with the discontinued indication statement: "treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy."

However, the situation with ENTRESTO is distinguishable from Velcade in several regards. The wording of the Velcade indication statement was simply edited to more concisely describe two mutually exclusive patient populations (first-line mantle cell lymphoma patients and second-line mantle cell lymphoma patients) in a single statement. FDA noted that its decision upon approval of the Velcade supplement to combine "first-line mantle cell lymphoma" and "second-line mantle cell lymphoma" in a single broad indication statement should not preclude approval of ANDA products that omit protected labeling:

> We note that the mantle cell lymphoma indications could have been written as "treatment of patients with mantle cell lymphoma who have received at least one prior therapy and treatment of patients with mantle cell lymphoma who have not received at least one prior therapy." If the indications had been written as such, then omission of the words describing the protected indication would result in "treatment of patients with mantle cell lymphoma who have received at least one prior therapy" and would presumably be allowable under the Petition's "only omissions" standard. We do not believe it would be appropriate for the scope of exclusivity for Velcade to be broadened due to the writing of labeling in a clear and concise manner.[82]

By contrast, the evolution of the ENTRESTO indication statement in adults reflects a considered decision by the agency to define the currently approved patient population in different terms than

[81] *See* FDA Petition Response regarding Velcade (bortezomib), Docket No. FDA-2017-P-3672-0022 (Nov. 6, 2017) (Velcade Petition Response) at 14-15, *available at* https://www.regulations.gov/document/FDA-2017-P-3672-0022.

[82] *Id.* at 15.

were used in the earlier iteration of the indication statement.[83] FDA elected not to use ejection fraction as a strict diagnostic cutoff or the "reduced ejection fraction" and "preserved ejection fraction" classifications. Instead, based on the previous approval in HFrEF patients and the results of the PARAGON-HF study, the agency approved ENTRESTO in all chronic heart failure patients, whether classified as having reduced ejection fraction or preserved ejection fraction. This is not a case of the agency merely combining first- and second-line patient populations "in a clear and concise manner" for the sake of brevity, as was done with Velcade, and the reasoning of the Velcade Petition Response therefore does not apply.[84]

Instead, as described above, the revised ENTRESTO indication statement represents an evolution in the agency's description of the approved patient population, as well as the relevance of LVEF as a diagnostic criterion. In fact, the agency determined – after careful consideration and discussion at the Advisory Committee meeting – not to use LVEF as a strict criterion for identifying patients that can benefit from ENTRESTO therapy. Rather, the changed indication statement captures the approval of ENTRESTO in all patients with heart failure, irrespective of their LVEF, but also advises practitioners that LVEF may be relevant to the anticipated treatment effect.

E. Conclusion

The new use approved in February 2021 for patients with chronic heart failure, including patients with preserved ejection fraction, is protected by both 3-year exclusivity and the HFpEF Patents listed in the *Orange Book*. Accordingly, an ANDA applicant seeking approval before the

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[83] In the sNDA submitted to FDA in April 2020 seeking to expand the approved patient population for ENTRESTO, Novartis proposed an indication statement that specifically referred to "heart failure with reduced ejection fraction" and "heart failure with preserved ejection fraction":

> ENTRESTO is indicated for the treatment of chronic heart failure:
>
> - To reduce cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction
> - To reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction with left ventricular ejection fraction below normal

See Novartis Presentations Briefing Information for the December 15, 2020 Meeting of the Cardiovascular and Renal Drugs Advisory Committee at 7, *available at* https://www.fda.gov/media/144448/download.

[84] Notably, the Velcade sponsor did not challenge FDA's petition denial in court. What is more, the agency never in fact approved an ANDA product with the labeling revisions described in the Velcade Petition Response. In related patent litigation, the Federal Circuit held that the proposed ANDA products would infringe a valid patent listed with Velcade, and the ANDA products that were the subject of the Velcade Petition Response were therefore not eligible for final approval. *See Millennium Pharms., Inc. v. Sandoz Inc*., 862 F.3d 1356, 1370 (Fed. Cir. 2017). Accordingly, the Velcade Petition Response does not represent binding authority or precedent for the agency.

expiration of the exclusivity must propose labeling that omits the exclusivity-protected conditions of approval and does not disclose the patented use, as described in the relevant Use Code.[85] An ANDA applicant may only seek approval for the conditions of use that existed in the ENTRESTO labeling prior to February 2021, *i.e.*, to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction.

However, there is no permissible way for ANDA applicants to draft an indication statement for use in patients with reduced ejection fraction by deleting words or making *de minimis* changes to the existing indication statement. FDA's "same labeling" regulations and the agency's longstanding interpretation of these regulations preclude the agency from adding language or making more than *de minimis* changes to the existing indication statement to omit ENTRESTO's protected use. Accordingly, the agency cannot approve an ANDA seeking to omit the patent- and exclusivity-protected use until expiration of the exclusivity in February 2024 – and even then, only if the ANDA applicants submit a paragraph IV certification to each of the HFpEF Patents.

IV. FDA SHOULD REFRAIN FROM APPROVING ANY ANDA THAT SEEKS TO OMIT THE PATENT-PROTECTED INFORMATION COVERINGs THE MODIFIED DOSING REGIMEN.

An ANDA applicant relying on ENTRESTO as the RLD may also seek to omit the modified dosing regimen in Section 2.5 by submitting a section viii statement to the '667 Patent. However, as described below, omitting the modified dosing regimen would render the proposed generic product less safe and effective than ENTRESTO for the remaining conditions of use. For this reason, the statute and governing regulations prohibit the agency from approving such an ANDA until the expiration of the '667 Patent. An ANDA applicant seeking approval before the expiration date of the '667 Patent must therefore submit a paragraph IV certification and include the modified dosing regimen in its labeling.[86] Novartis has initiated litigation against 11 ANDA applicants who apparently have already determined that the modified dosing regimen must be included in their labeling and thus provided notice to Novartis of paragraph IV certifications to the *Orange Book* listed dosing patent.

A. The Section 2.5 Dosing Regimen is Protected by the '667 Patent.

Following issuance of the '667 Patent on July 13, 2021, Novartis timely submitted information to list the patent in the *Orange Book.* The '667 Patent is listed with the following Use Code:

[85] As previously noted, an ANDA applicant seeking approval during the 3-year exclusivity period would also have to submit a section viii statement with regard to the HFpEF Patents.

[86] At least 11 ANDA applicants have provided notice to Novartis regarding paragraph IV certifications to the '667 Patent.

> TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE.[87]

Thus, for HFrEF patients, the '667 Use Code covers the modified dosing regimen described in Section 2.5, which directs the use of a starting dose of 24/26 mg (sacubitril/valsartan) twice daily for adult patients who are not taking an ACE inhibitor or an ARB (ACE inhibitor or ARB-naïve), or who were previously taking low doses of these agents. Section 2.5 further instructs physicians and patients to increase the dose every 2 to 4 weeks, and then to follow the standard dosing regimen described in Section 2.1. For pediatric patients who are not taking an ACE inhibitor or an ARB, or who were previously taking low doses of these agents, the modified dosing regimen in Section 2.5 provides that ENTRESTO should be initiated for these patients at half the standard recommended dose and then up-titrated every 2 weeks.

An ANDA applicant seeking to submit a section viii statement to the '667 Patent must omit the information for adult HFrEF patients and for pediatric HFrEF patients weighing more than 50 kg in Section 2.5. To include the information regarding the modified dosing regimen would impermissibly disclose the protected condition of use, as described in the Use Code.

B. Omitting the Modified Dosing Regimen Would Render an ANDA Product Less Safe and Effective than ENTRESTO.

Omission of the patent-protected information in Section 2.5 would render an ANDA product less safe and effective than ENTRESTO for the remaining conditions of use. As a result, FDA may not approve an ANDA applicant that seeks to omit this information – and submits a corresponding section viii statement – until expiration of the '667 Patent.

The modified dosing regimen for patients who are ACE inhibitor or ARB-naïve, or who were previously on a low dose of these agents, has been in the ENTRESTO labeling since initial approval in 2015.[88] If the modified dosing regimen were omitted from the labeling of generic versions of ENTRESTO, HFrEF patients who are ACE inhibitor or ARB-naïve, or who previously received a low dose of these agents, would be administered a generic sacubitril and valsartan product under the standard titration schedule provided for in Section 2.1 of the ENTRESTO labeling – including both a higher starting dose and more rapid titration schedule than is recommended for such patients. Use of the standard dosing regimen would likely increase the

[87] Electronic *Orange Book*, Patent and Exclusivity Listing for NDA 207620.

[88] The only changes to this section since initial approval have been the incorporation of pediatric dosing recommendations following approval of the use in pediatric patients on October 1, 2019, and editorial changes incorporated following approval of the expanded indication on February 16, 2021.

rates of clinically significant adverse events in this patient population and could also result in decreased efficacy, if patients discontinue treatment prematurely or remain on a lower dose before advancing to the labeled target maintenance dose (*e.g.*, due to adverse events).

The modified dosing regimen in Section 2.5 is derived from the results of the TITRATION study conducted by Novartis. The TITRATION study evaluated multiple dosing regimens in a broader range of patients than had been enrolled in PARADIGM-HF. Specifically, TITRATION included patients who had not taken ACE inhibitors or ARBs, or who were previously taking low doses of these agents. Among these patients, the TITRATION study showed that those treated with sacubitril and valsartan at the standard dose and titration schedule experienced higher rates of hypotension, renal dysfunction, and hyperkalemia than the patients on modified dosing regimens.[89] For this reason, the Division concluded that "[a] longer titration period with a starting dose of 50 mg bid may reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an [ACE inhibitor] or ARB," as well as patients who are ACE inhibitor or ARB-naïve.[90]

Accordingly, generic drug labeling that omits the modified dosing regimen would fail to inform patients and providers of the safest option for administering sacubitril and valsartan to HFrEF patients who are ACE inhibitor or ARB-naïve, or who previously received a low dose of these agents, which would result in higher rates of adverse events in this group. The dangers posed by hypotension, renal dysfunction, and hyperkalemia to heart failure patients are severe. Patients with renal dysfunction are at a 50% increased relative mortality risk compared to patients with normal renal function, a particularly notable metric for patients on low doses of ACE inhibitors and ARBs who may already be experiencing renal dysfunction.[91] Additionally, hyperkalemia has been consistently linked to poor clinical outcomes in patients with heart failure.[92] The modified dosing regimen is therefore critical to ensure that HFrEF patients who are ACE inhibitor or ARB-naïve, or who previously received a low dose of these agents, are able to tolerate a sacubitril and valsartan product without experiencing clinically relevant adverse events that could impact their treatment.[93]

Moreover, these adverse events could also prevent patients who are ACE inhibitor or ARB-naïve, or who previously received a low dose of these agents, from achieving the target treatment dose

[89] *See* Senni at 1198-1201.

[90] 2015 Clinical Review at 70.

[91] G. Smith, *et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis.* J. AM. COLLEGE OF CARDIO. 2006;47:1987, 1994 (Tab H); W. Ouwerkerk, *et al., Determinants and clinical outcome of uptritration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study,* EUR. HEART J. 2017;38:1883, 1884 (Tab I).

[92] *See, e.g.*, M. Fudim, *et al., Hyperkalemia in Heart Failure: Probably Not O"K"*, J. AM. HEART ASSOC. 2018;7:1, 1 (Tab J).

[93] *See* Senni at 1201.

and thereby receiving the full benefits of sacubitril and valsartan therapy. It is well known that adverse events are a significant factor in treatment adherence. For example, hypotension is often cited as an important factor limiting patients' use of life-saving heart failure treatments.[94] Given the relationship between adverse events and treatment adherence, it is critical that labeling directs providers and patients to initiate treatment in the safest and best-tolerated manner.

Although additional warnings in the ENTRESTO labeling address dosing adjustments for patients experiencing hypotension, renal dysfunction, and hyperkalemia, they do not direct providers on how to initiate treatment with sacubitril and valsartan or titrate to the recommended maintenance dose. Further, these warnings do not specifically identify patients previously taking a low dose of an ACE inhibitor or ARB, or patients naïve to these agents, as a group that may be vulnerable to these adverse events. In contrast, the modified dosing subsection of the labeling signals to patients and providers that the standard ENTRESTO dosing schedule could put ACE inhibitor or ARB-naïve patients at risk.

The protected dosing regimen in Section 2.5 provides clear directions for patients and providers so that ENTRESTO is administered at a safe dose and tolerable schedule to a group of patients who may otherwise fail to achieve the target dose. The absence of this information would increase the likelihood of these patients experiencing clinically important adverse events that could jeopardize their health and prevent them from experiencing the full benefits of ENTRESTO. The omission of this dosing regimen from the labeling of any ANDA product would render that product less safe and effective than ENTRESTO, and should not be permitted.

C. Refusing to Permit ANDA Applicants to Omit the Modified Dosing Regimen would be Consistent with Agency Precedent.

In three similar scenarios, FDA has refused to permit generics to omit protected information related to dosing adjustments, to ensure the safety of the proposed generic products for the remaining, non-protected conditions of use.

The first case involved exclusivity-protected dosing information for Colcrys (colchicine), a drug approved for the prophylaxis of gout flares and the treatment of acute gout flares. The protected information at issue related to dosing information and dose adjustment recommendations when treating patients with acute gout flares, to prevent unnecessary toxicity when colchicine is co-administered with certain other drugs. In a 2011 citizen petition response, FDA determined that sponsors of generic colchicine products must include in their labeling the information on dose

[94] J. Cautela, *et al., Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients*, EURO. J. HEART FAIL. 2020; 22:1357, 1358 (Tab K). For example, in PARAGON-HF, adverse events led to permanent discontinuation of ~20% of the safety population. Hypotension was the most common adverse event resulting in discontinuation. 2021 Clinical Review at 72.

adjustment for gout flares, even if they omitted the acute gout flare indication.[95] Health care professionals familiar with the drug might recommend using the generic for the treatment of an acute flare, even when the acute flare indication and dosing information had been specifically omitted by the generic. In that circumstance, the generic would be unsafe because it would lack adequate dosing instructions and important drug-drug interaction information. Patients would be prescribed and guided to use the drug, but without adequate information on dose adjustment if those patients fell within the omitted condition of use. Therefore, the agency concluded that the generic products must include the protected dose-adjustment information in their labeling.[96]

In another similar precedent, FDA again prohibited ANDA applicants from omitting protected sections of the RLD's labeling related to DDI studies and a modified dosing regimen. In 2016, Jazz Pharmaceuticals (Jazz) submitted a citizen petition requesting that FDA refrain from approving generic versions of Xyrem (sodium oxybate) that did not include in the proposed labeling patent-protected DDI information related to concomitant use of sodium oxybate and divalproex sodium.[97]

Xyrem was first approved in 2002. DDI studies conducted by the sponsor showed that coadministration of Xyrem with divalproex sodium increased mean systemic exposure to sodium oxybate such that patients would be at an increased risk of central nervous system depression, which could prove fatal.[98] FDA rightfully concluded that this information and the resulting dosing recommendations were important to prevent potentially life-threatening events and that prescribers would be unaware of the risks associated with the coadministration in the absence of the dosing recommendations in the generic labeling. As a result, the agency determined that the omission of the DDI information and associated dose reductions would render a proposed generic product less safe than Xyrem for the remaining, unprotected conditions of use.[99]

Most recently, Taiho Oncology, Inc. (Taiho) submitted a citizen petition requesting that FDA prohibit ANDA applicants referencing Lonsurf (trifluridine and tipiracil) from omitting portions of the Lonsurf labeling that describe dosage reduction instructions for patients with renal impairment.[100] Lonsurf is indicated for patients with metastatic colorectal cancer and gastric or gastroesophageal junction adenocarcinoma who have disease progression on or after prior therapy.

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[95] FDA Petition Response regarding Colcrys (colchicine), Docket No. FDA-2010-P-0614-0072 (May 25, 2011), *available at* https://www.regulations.gov/document/FDA-2010-P-0614-0072.

[96] *Id*. at 24.

[97] FDA Petition Response regarding Xyrem (sodium oxybate), Docket No. FDA-2016-P-2672 (Jan. 17, 2017), *available at* https://www.regulations.gov/document/FDA-2016-P-2672-0019.

[98] *Id.* at 2.

[99] *Id.* at 4-5.

[100] FDA Petition Response regarding Lonsurf (trifluridine and tipiracil), Docket No. FDA-2022-P-0155 (Feb. 10, 2022), *available at* https://www.regulations.gov/document/FDA-2022-P-0155-0006.

The standard of care therapies for patients with the indicated cancers have the potential to cause renal impairment, which means that any patient within the scope of the generic's conditions of use is at risk of experiencing worsening renal function. Taiho conducted a post-marketing study evaluating dosing recommendations for patients with varying degrees of renal impairment, based on the understanding that systemic exposure of the drugs would increase significantly with worsening renal function. The study confirmed that patients with severe renal impairment should be given a reduced dose of Lonsurf to achieve the same efficacy as the standard dose while limiting serious adverse effects from excess exposure levels, particularly those associated with the trifluridine active ingredient. The sponsor updated the labeling to include reduced dose recommendations for patients with severe renal impairment, as measured by creatinine clearance. In a subsequent citizen petition, the Lonsurf sponsor argued that omission of these recommendations would render generic drugs less safe than Lonsurf for the remaining nonprotected conditions of use (i.e., for use in patients without severe renal impairment).

In a July 2022 petition response, FDA agreed that the dosing regimen for severe renal impairment served as an "important signal to health care professionals" to closely and systematically monitor the renal function of patients taking Lonsurf, and thus was necessary to the safe use and administration of trifluridine and tipiracil for all patients (including those not presently experiencing severe renal impairment).[101] A generic that omitted the dosing regimen from the labeling would continue to share the same indication statement as Lonsurf, which includes patients who may develop severe renal impairment during the course of treatment. Importantly, the agency rejected the argument offered on behalf of various generic drug sponsors that the omission of the dosing instructions would establish (by inference) that the generics were not approved for use in patients with severe renal function.[102] Based on this line of reasoning, if a patient were to present with or progress to severe renal impairment, the health care provider would know that the generic was not indicated or otherwise labeled for such a patient. In such a case, the patient would be prescribed the fully labeled reference product instead of the generic.

The agency thoroughly rejected this argument, finding that without this information in the labeling, health care professionals may not know that renal function (which may change over time) is an important factor in the dosing and administration of the drug product.[103] Nor did the agency permit the generics to add new information to their labeling to specifically exclude patients with severe renal impairment from using the generic products.

In both the Colcrys and Lonsurf cases, the agency recognized that patients who are appropriately prescribed the generic products may, at some point in the course of their treatment, be guided by a health care professional to use the drug for the omitted use without the necessary dose adjustment

[101] *Id.* at 14.

[102] *Id.* at 11 and 15.

[103] *Id.* at 15.

information (Colcrys), or they may use the drug after they have developed a dose-limiting condition without the necessary dose adjustment information (Lonsurf). With ENTRESTO, if the dose modification for ACE inhibitor or ARB-naïve patients were omitted, the generic drugs would be unsafe for their remaining conditions of use because ACE inhibitor or ARB-naïve patients would fall within the on-label population for the generic products, *i.e.,* Adult Heart Failure patients.[104] As such, they would be dosed at the recommended starting dose and titration schedule for the general Adult Heart Failure patient population – a starting dose and schedule that is known to place these patients at unnecessary risk of harm. As shown by the Colcrys, Xyrem, and Lonsurf cases, the omission of dosing information for patients who could fall within the on-label population for a proposed generic product, to protect those patients from preventable risks, has not been permitted by the agency.

In the case of ENTRESTO, the TITRATION study provided critical new information on the safety and tolerability of initiating sacubitril and valsartan in HFrEF patients not currently taking an ACE inhibitor or ARB, or on a low dose of these agents. The TITRATION study demonstrated that a lower starting dose and more gradual titration schedule resulted in fewer clinically relevant adverse events, including hypotension, renal dysfunction, and hyperkalemia. This information has been included in the ENTRESTO labeling since its initial approval and signals to prescribers to appropriately screen patients prior to initiating treatment. Without this information prominently stated in the labeling (as it is for ENTRESTO), ACE inhibitor or ARB-naïve patients would fall within the general Adult Heart Failure population under Section 2.2 of the labeling, and would be dosed in a manner contrary to the findings of the TITRATION study.

In sum, a generic product that omits the ENTRESTO dose adjustment labeling is unsafe for its remaining conditions of use because ACE inhibitor or ARB-naïve patients would remain within the scope of the indication statement for whom the generic products would be indicated and would be dosed and titrated without the information needed to reduce the risk of serious health complications. As made clear in the Lonsurf decision, generic sponsors cannot add language to the labeling to omit the ACE inhibitor and ARB-naïve heart failure patients from the on-label patient population. Nor could it be inferred that this group would fall outside the remaining conditions of use. If the dose modification information were omitted from the generic products, these patients would receive treatment according to the standard Adult Heart Failure dosing recommendations and would be titrated up more quickly than is tolerable, which would jeopardize their safety and result in treatment failure for those required to discontinue treatment. The prevailing precedent, as discussed here, decisively shows that such an outcome has not been considered acceptable by the agency under the governing regulatory standard. It should not be considered acceptable here.

[104] ENTRESTO Prescribing Information, Section 2.2.

D. FDA Should Refrain from Approving an ANDA Product that Seeks to Omit the Protected Dosing Regimen in Section 2.5.

ANDA applicants relying on ENTRESTO as the RLD should not be permitted to submit a section viii statement to the '667 Patent. The resulting omission of the modified dosing regimen for HFrEF patients from Section 2.5 would render the generic product less safe and effective than ENTRESTO for the remaining conditions of use. Alternatively, ANDA applicants can elect to defer final approval until expiration of the '667 Patent or to submit a paragraph IV certification to this patent.

CONCLUSION

For the reasons described above, FDA should refrain from approving an ANDA product that seeks to omit the patent- and exclusivity-protected use approved in 2021 until expiration of the 3-year exclusivity in February 2024. At that time, an ANDA applicant can seek approval for this use by submitting a paragraph IV certification to the HFpEF Patents and including the protected use in its labeling. An ANDA applicant cannot obtain approval – even after the expiration of the 3-year exclusivity – by submitting a section viii statement to the HFpEF Patents and omitting the patent-protected use.

Similarly, FDA should refrain from approving an ANDA that contains a section viii statement to the '667 Patent and seeks to omit the modified dosing regimen for HFrEF patients in Section 2.5, until the expiration of this patent, because that omission would render the ANDA product less safe and effective than ENTRESTO for the remaining conditions of use. ANDA applicants must instead submit a paragraph IV certification to the '667 Patent and include this information in their proposed labeling.

ENVIRONMENTAL IMPACT

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

ECONOMIC IMPACT

Pursuant to 21 CFR 10.30(b), an economic impact statement 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: February 16, 2021 (approval of supplement to ENTRESTO NDA for new use); March 16, 2021 (submission of US Patent Nos. 9,517,226 and 9,937,143 for listing in the *Orange* Book); July 13, 2021 (issuance of US Patent No. 11,058,667 claiming modified dosing regimen); October 5, 2021 (issuance of US Patent No. 11,135,192); April 29, 2022 (receipt of FDA response to November 30, 2021 citizen petition). 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: Novartis Pharmaceuticals Corporation. 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,

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