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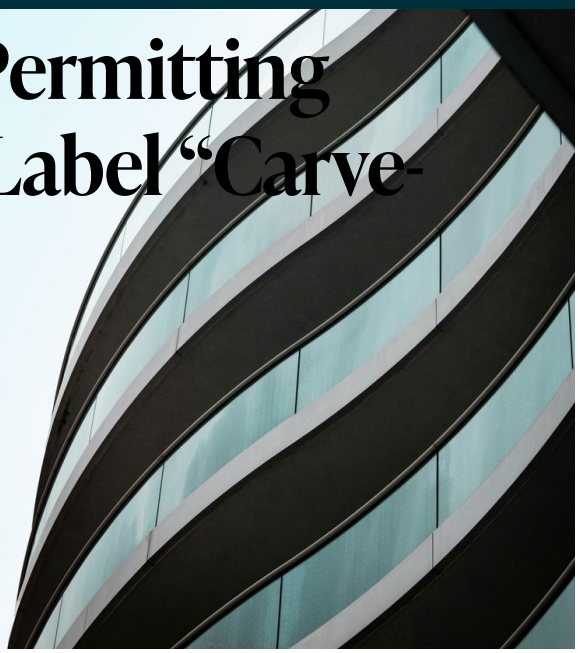
FDA Expands Practice of Permitting Population-Based Skinny Label "Carve-Ins"



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July 30, 2024, 8:27 AM
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FDA recently doubled down on its approach of allowing new language in an ANDA label as the result of a section viii statement – a so-called "carve-in." Section viii statements assert that an ANDA does not seek approval for a method of use covered by patent or exclusivity. This of course generally requires omitting protected information from the label. But in a recent response to a citizen petition, FDA permitted adding new language to an indication in conjunction with a section viii statement. There is some precedent for this. FDA previously allowed a "carve-in" that reverted to a previously approved indication covering a narrower patient population.[1] But here, FDA endorsed excluding a protected population by adding new labeling language that is not present in the currently approved indication.

The drug at issue here is Entresto (sacubitril/valsartan), which is used for the treatment of chronic heart failure. In its initial clinical studies to support approval, the RLD holder only included patients with reduced left ventricular ejection fraction ("LVEF"). However, a subsequent study also included some patients with an LVEF within the normal range. FDA thus approved a new version of the indication that expanded the approved patient population. In addition to the three-year exclusivity associated with the new clinical trial (since expired) the RLD holder also listed patents in the Orange Book purporting to claim this new patient population. The RLD holder then filed the instant citizen petition asking, among other things, that FDA not approve any ANDA seeking to exclude the newly added patient population using section viii statements.

FDA rejected the action requested by the citizen petition and explicitly endorsed a labeling "carve-in" that ANDA applicants might use, as shown below:

Revisions to Entresto's Previously Approved Adult HF Indication Statement	Entresto's Current Approved Adult HF Indication Statement	FDA's Suggested "Carve-in"
1.1 Adult Heart Failure Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in **adult** patients with chronic heart failure ~~(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 *[see Clinical Studies (14.1)]*.**	**1.1 Adult Heart Failure** Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies (14.1)]*.	**1.1 Adult Heart Failure** Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure~~.~~ **and reduced ejection fraction.** ~~Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.~~ ~~LVEF~~**Left ventricular ejection fraction (LVEF)** is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies (14.1)].

Indeed, at least one ANDA filer has already been approved with such a "carve-in." MSN's ANDA No. 213748 referencing Entresto was approved on July 24, 2024, the same day FDA issued its response to the citizen petition.[2]

Overall, FDA's approach here is consistent with its earlier Velcade decision. There, FDA allowed a "carve-in" with an older version of an indication with added language that limited the patient population to second-line lymphoma patients. Likewise, in this case, "the Agency does not believe it would be appropriate for the scope of patent protection for Entresto to be broadened due to the writing of labeling in a clear and concise manner."[3] Instead, FDA here permits some sparing modification of the current indication with additional terms. This is a slight extension of FDA's approach in Velcade, which simply used a previously approved version of the indication. FDA's response here may signal some flexibility by the Agency to

consider novel “carve-in” labeling modifications as part of a section viii skinny labeling strategies.

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

[2] *See also* FDA Docket No. FDA-2022-P-2228, FDA Response to Citizen Petition regarding Entresto (sacubitril and cvalsartan), at 2 n.6 (Jul. 24, 2024), available at https://www.regulations.gov/document/FDA-2022-P-2228-0015.

[3] *Id.* at 38 (cleaned up).

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