DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 10/25/16

TO: E-Z-HD (Barium Sulfate) For Oral Suspension File (NDA 208036)

FROM: CDER Exclusivity Board

SUBJECT: Five-Year Exclusivity Recommendation for E-Z-HD (Barium Sulfate) For Oral Suspension (NDA 208036)

SUMMARY

This memorandum addresses whether E-Z-HD (barium sulfate) for oral suspension (NDA 208036), approved on January 11, 2016, comprises a drug substance that contains no active moiety that has been previously approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and thereby qualifies for 5-year new chemical entity (NCE) exclusivity.[1]

Upon review of the regulatory documents related to NDA 208036 and other relevant documents, the Exclusivity Board (Board) within the Center for Drug Evaluation and Research (CDER) has determined that the drug substance (or active ingredient) contained in E-Z-HD, barium sulfate, contains the active moiety barium, which has been previously approved by FDA in an application submitted under section 505(b) of the FD&C Act. Accordingly, the Board recommends that E-Z-HD be deemed ineligible for 5-year NCE exclusivity.

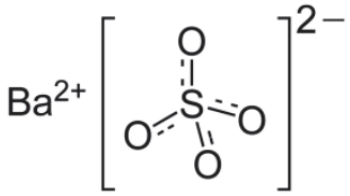
A discussion of the Board's reasoning follows.

I. FACTUAL AND PROCEDURAL BACKGROUND

On December 11, 2014, Bracco Diagnostics Inc. submitted NDA 208036 for E-Z-HD (barium sulfate) for oral suspension. E-Z-HD is a radiographic contrast agent indicated for use in double-

[1] See sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act; see also 21 CFR 314.108(a).

contrast radiographic examinations of the esophagus, stomach, and duodenum to help visualize the gastrointestinal (GI) tract in patients 12 years and older.[2] E-Z-HD is supplied as a fine white powder for oral suspension (98% w/w barium sulfate) for oral administration. The active ingredient, barium sulfate, is designated chemically as $BaSO_4$, with a molecular weight of 233.43 grams(g)/mole, and a density of 4.5 g/cm^3.[3] Barium sulfate is the sulfate salt of barium, an alkaline earth, divalent metal. The chemical structure is below.



Barium sulfate is classified pharmacologically as a radiologic contrast agent, (b) (4) Due to its high atomic number, barium is opaque to X-rays and therefore acts as a positive contrast agent for radiographic studies.[5] As described in the Cross-Discipline Team Leader (CDTL) Review of the E-Z-HD NDA, barium sulfate has been used to opacify the GI tract since the early 1900s.[6]

At least one drug product, Metabarin, containing barium sulfate as its active ingredient has been previously marketed under an NDA in the United States. On December 2, 1948, C.S.C. Pharmaceuticals, a division of Commercial Solvents Corporation, submitted an application (NDA 6624) for Metabarin under section 505(b) of the FD&C Act. The application became effective on December 9, 1948.[7,8] As described in NDA 6624, Metabarin, an oral suspension, is a barium contrast medium used in the roentgenographic (X-ray) visualization of the esophagus, stomach, and intestinal tract.[9] The NDA indicates that Metabarin contains 99.656% barium sulfate (USP) along with a suspending agent, intended to provide a high degree of dispersibility,

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[2] See E-Z-HD Labeling, Section 1, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208036s000lbl.pdf.

[3] See E-Z-HD Labeling, Section 11.

[4] See NDA 208036, Division Director Summary Review (Jan. 4, 2016) at 2 and 6.

[5] See E-Z-HD Labeling, Section 12.1.

[6] NDA 208036, CDTL Review, (Jan. 4, 2016) at 2.

[7] Under the FD&C Act in effect in 1948, NDAs submitted to FDA "bec[a]me effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpone[d] the effective date of the application to such time . . . as the Secretary deem[ed] necessary to enable him to study and investigate the application." See section 505(c) of the FD&C Act of 1938 (Pub. L. 75-717). In the 1962 Amendments to the FD&C Act, such applications, which had "become effective" based, in part, on a demonstration of safety, were "deemed approved." See section 107(c)(2) of the 1962 Amendments (Pub. L. 87-781).

[8] A Notice of Opportunity for Hearing was published in 1970 proposing to withdraw approval of NDA 6624 (along with several other NDAs) on the grounds that the NDA-holders failed to make required reports under section 505(j) of the FD&C Act in effect at the time. 35 FR 2674 (Feb. 6, 1970). Receiving no requests for a hearing on the proposed withdrawal of approval of NDA 6624, later that year, FDA withdrew approval by notice in the Federal Register. 35 FR 11929 (July 24, 1970).

[9] NDA 6624, Diagnostic Advantages, at 4; see also Metabarin Labeling.

and two flavoring agents.[10] The Metabarin labeling states that Metabarin is (b) (4) [redacted]

II. STATUTORY AND REGULATORY BACKGROUND

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an application submitted under Section 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective under the conditions of use described in the labeling.[12] The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) described abbreviated pathways for approval of drug products that allow an applicant to rely to the maximum extent possible on what is already known about a drug. These are described in sections 505(b)(2) (which established the 505(b)(2) application pathway) and 505(j) (which established the Abbreviated New Drug Application (ANDA) pathway) of the FD&C Act.[13] At the same time, the Hatch-Waxman Amendments provided incentives for pharmaceutical innovation, including exclusivity to protect certain products from competition for specified periods of time.

Sections 505(j)(5)(F)(ii) and (c)(3)(E)(ii) of the FD&C Act describe a 5-year exclusivity period for certain drugs, during which 505(j) and 505(b)(2) applications may not be submitted for review (i.e., 5-year NCE exclusivity). Specifically, Section 505(j)(5)(F)(ii) of the FD&C Act provides, in relevant part, as follows:

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section . . . .[14]

FDA's regulations implementing the 5-year NCE provision of the Hatch-Waxman Amendments, at 21 CFR 314.108, provide that:

> If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that

[10] NDA 6624, Part 3 (A Full Statement of the Composition of Metabarin) at 1 and Part 4(a) (A Full Description of the Methods Used in the Manufacture, Processing, and Packing of Metabarin) at 1.

[11] NDA 6624, Diagnostic Advantages at 4.

[12] Section 505(b)(1) of the FD&C Act.

[13] The precise nature of, and requirements established by, these pathways are not relevant to our analysis of and conclusions with regard to the issues discussed in this recommendation.

[14] See also section 505(c)(3)(E)(ii) of the FD&C Act (containing the same language for 505(b)(2) applications).

> contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application . . . .[15]

The regulations define "new chemical entity" as:

> [A] drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act."[16]

"Active moiety," in turn, is defined as:

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[17]

"Approved under section 505(b)" is defined as:

> [A]n application submitted under section 505(b) and approved on or after October 10, 1962, or an application that was "deemed approved" under section 107(c)(2) of Pub. L. 87-781.[18]

In the Agency's regulations governing new drug applications, FDA has defined "drug product" as:

> [A] finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.[19]

In the same regulation, "drug substance" is defined as:

> [A]n active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use [sic] in the synthesis of such ingredient.[20]

III. DISCUSSION

The FD&C Act and FDA's regulations preclude eligibility for 5-year NCE exclusivity when the drug contains an active moiety that has been previously approved in an application under section

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[15] 21 CFR 314.108(b)(2).

[16] 21 CFR 314.108(a).

[17] Id.

[18] Id.

[19] 21 CFR 314.3(b).

[20] Id.

505(b) of the FD&C Act. E-Z-HD contains barium sulfate, the sulfate salt of barium, as its active ingredient. The active moiety in E-Z-HD is barium.[21] Likewise, barium sulfate is the active ingredient and barium is the active moiety in Metabarin. As noted above, the NDA for Metabarin became effective in 1948 and was deemed approved through the 1962 Amendments to the FD&C Act. FDA's regulations make clear that a drug product that is the subject of an application that was "deemed approved" under the 1962 Amendments is considered to be approved in an application under section 505(b) of the FD&C Act for purposes of determining whether certain products qualify for 5-year NCE exclusivity under section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act.[22] Therefore, because the active moiety in E-Z-HD has been previously approved in an application under section 505(b) of the FD&C Act, i.e., the Metabarin NDA, E-Z-HD does not contain a new chemical entity and is not eligible for 5-year NCE exclusivity.

IV. CONCLUSION

For the reasons described above, and notwithstanding any prior assessments made,[23] the Board has determined that the active moiety in E-Z-HD has been previously approved. Accordingly, the Board recommends that E-Z-HD be deemed ineligible for 5-year NCE exclusivity. The Board further recommends that the Exclusivity Summary for E-Z-HD be revised to reflect the analysis in this memorandum.[24]

Sanjay Sitlani -A

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[21] Under 21 CFR 314.108(a), the active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester or salt. Upon excluding the sulfate salt anion, the resulting active moiety is barium.

[22] Id.

[23] See, e.g., NDA 208036, RPM Filing Review, classifying the NDA as Type 7 for Drug Already Marketed Without an Approved NDA.

[24] The application was based solely on published literature, marketing surveillance, and publicly available information on barium sulfate products; no preclinical or clinical studies were conducted or sponsored by the applicant for approval of this application. See NDA 208036, CDTL Review at 2. Therefore, this application is also not eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act.

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/s/

FRANK A LUTTERODT
10/25/2016