CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208036Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # **208036**	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: **EZ-HD** Established/Proper Name: **Barium Sulfate** Dosage Form: **Powder for oral suspension** Strengths: **98% w/w (reconstitution with water yields approximately 140 mL of an oral suspension containing 2.38 grams barium sulfate per mL)**		
Applicant: **Bracco Diagnostics Inc.**		
Date of Receipt: **December 11, 2014**		
PDUFA Goal Date: **January 11, 2016**	Action Goal Date (if different):	
RPM: **Frank Lutterodt**		
Proposed Indication(s): **For use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum** (b) (4)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	**All sections of labeling except section 11 Description and section 16 How Supplied**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Barium sulfate is an insoluble compound and is biologically inert. The systemic absorption of barium sulfate is extremely limited (greater than 99.99% of the dose is not absorbed); it is not metabolized and is eliminated unchanged in the feces. Barium sulfate itself has no pharmacological effects.

The relied upon literature describes products that contain the same active ingredient (barium sulfate) and in similar dose ranges as that proposed by the applicant. In addition, OPQ evaluated the comparability of the proposed product to the historical, commercially available barium sulfate products described in the literature. OPQ determined that the critical quality attributes of dual barium sulfate particle size (b) (4) and viscosity, which are significant for clinical performance, were similar from the time of product introduction through the changes to the barium sulfate/excipient/container suppliers and until the current time. Therefore, the products are considered comparable from a quality perspective.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK A LUTTERODT
01/10/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 5, 2016

To: Frank Lutterodt
Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D., RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 208036 E-Z-HD (barium sulfate) injection, for oral suspension**

In response to your consult dated April 16, 2015, we have reviewed the draft prescribing information (PI) for E-Z-HD (barium sulfate) injection, for oral suspension (E-Z-HD). OPDP has reviewed the substantially complete version of the PI titled "BaSO4 EZ-HDlabeling – LDT recommendations – 12 22 15" sent via email from Frank Lutterodt to OPDP on December 30, 2015. We had comments for sections 5.1, 5.6, 5.7, and 6 of the PI which are included directly on the attached copy of the labeling.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADAM N GEORGE
01/05/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Mona Khurana, M.D., Medical Officer
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV

Through: Hari Cheryl Sachs, M.D., Team Leader

Linda Lewis, M.D., Acting Deputy Director

To: Division of Medical Imaging Products

Drug: E-Z-HD (98% Barium Sulfate Suspension)

Application number: NDA 208036 (IND 115090)

Subject: Review Pediatric Survey Data

Applicant: Bracco Diagnostics Inc.

Materials Reviewed:

- Documents entered into DARRTS related to new drug application (NDA) 208036
  - 8/16/15 Medical Officer Review of NDA 208036 (Brenda Q. Ye; Reference ID 3810025)
  - 5/27/15 FDA Information Request (Reference ID 3766366)
  - 7/27/15 Preliminary Comments (Reference ID 3798126)
  - 7/30/15 Type A Meeting Minutes (Reference ID 3812611)
- Documents entered into DARRTS related to pre-investigational new drug (PIND) 115090
  - 8/3/12 Type C Pre-IND Meeting Minutes (Reference ID 3169433)
  - 11/25/13 Type C Preliminary Meeting Comments (Reference ID 3412418)
  - 11/26/13 Medical Officer Review of Type B Pre-NDA Meeting Request (Barbara A. Stinson; Reference ID 3413591)
  - 11/21/14 Type A meeting Minutes (Reference ID 3662390)
  - 8/31/15 Request for Deferral of Pediatric Studies for NDA 208143
- Documents entered into DARRTS related to NDA 208143
  - 9/1/15 DPMH Memorandum (Carrie Ceresa; Reference ID 3813908)

Consult Request

The Division of Medical Imaging Products (DMIP) consulted the Division of Pediatric and Maternal Health (DPMH) for assistance in reviewing pediatric survey data submitted by the applicant and to opine on the adequacy of the data to support approval of E-Z-HD for pediatric use.

I. Background

Different barium sulfate formulations containing purified barium conforming to U.S. Pharmacopeia standards have been used to opacify the gastrointestinal (GI) tract since the early 1900s. However, all barium sulfate products used as diagnostic medical imaging agents have been marketed to date as unapproved drugs in the United States.

(b) (4)

II. Regulatory History of this Application

FDA received the first two (b) (4) applications in December 2014. These included 505(b)(2) NDA submissions for E-Z-HD (NDA 208036) and Readi-Cat 2/Readi-Cat 2 Smoothie (NDA 208143). The E-Z-HD NDA was submitted on December 11, 2014 for a 98% barium sulfate suspension proposed for use in double contrast radiography of the upper gastrointestinal tract (UGI). The Readi-Cat 2 NDA was submitted on December 18, 2014 for 2% barium sulfate suspensions proposed for use with computed tomography (CT) of the abdomen (b) (4) . Both NDAs are exclusively literature-based and rely on the following information:

- Published peer-reviewed articles and reviews
- Post-marketing data
- Professional guidelines issued by the American College of Radiology and European Society of Urogenital Radiology (ESUR)

The E-Z-HD ND (b) (4) to be filed with FDA for barium sulfate.

DPMH Comments:

- *Both NDAs are required to provide a pediatric assessment under the Pediatric Research Equity Act (PREA) since both products are considered new active ingredients. They were previously marketed as unapproved drugs.*

[1] 11/26/13 Medical Officer Review of Type B Pre-NDA Meeting Request (Barbara A. Stinson; DARRTS Reference ID 3413591)

[2] 8/16/15 Medical Officer Review of NDA 208036 (Brenda Q. Ye; DARRTS Reference ID 3810025)

The applicant did not submit an initial pediatric study plan (iPSP) prior to submission of either NDA. DMIP filed both NDAs without agreed upon iPSPs because of the need to review marketed unapproved drugs products. (b) (4)

- There is limited applicability of E-Z-HD use in the pediatric population for the double contrast examinations of the esophagus and UGI tract (i.e., studies would be impossible or highly impracticable). The applicant stated that such examinations are very rarely performed in pediatric patients and are more difficult to perform in pediatric patients because of the needs for patient cooperation, ingestion of an effervescent agent, and use of a high density barium contrast agent. The applicant also stated double-contrast examinations are associated with higher radiation doses and are generally used in conditions less common to pediatric patients.
- The applicant needs to gather further evidence on the clinical use and medical need of Readi-Cat 2 and Readi-Cat 2 Smoothie for the CT imaging indication.

DPMH Comments: DPMH was previously consulted to participate in labeling discussions for both NDAs.[3] DPMH acknowledged that use of E-Z-HD is low in pediatric patients and, therefore, agreed with DMIP that a full pediatric waiver may be requested for E-Z-HD based on the fact that studies would be impossible or highly impracticable but that the applicant must justify this reason for a waiver request with any available information. (b) (4) *DPMH noted that efficacy extrapolation from adults to pediatric patients would likely be acceptable for CT imaging and that sufficient published data could be obtained to inform pediatric dosing and safety, obviating the need for additional clinical studies. DPMH recommended the applicant perform the literature review before NDA approval in order to determine whether Readi-Cat 2/Smoothie may be fully labeled for use in all pediatric populations. If the data are sufficient to support a full pediatric assessment then DPMH stated no deferred studies under PREA would be required.*

FDA issued an Information Request (IR) to the applicant on May 27, 2015 informing them that they must submit an iPSP within 30 days of the date of the letter.[4] At a subsequent Type A meeting, the applicant proposed conducting a survey among current users and medical experts of barium sulfate products in pediatric patients to confirm how these products are used and to obtain information necessary to finalize their iPSP such as age subgroups, methods of use, dosing, indications for use, and special precautions.[5] FDA and the applicant agreed that the applicant would submit the survey data, supporting the iPSP for all barium sulfate products, to the (b) (4) E-Z-HD NDA by the Prescription Drugs User Fee Act (PDUFA) action goal date of October 11, 2015. FDA noted that these survey

[3] 9/1/15 DPMH Memorandum (Carrie Ceresa; Reference ID 3813908)

[4] 5/27/15 FDA Information Request (DARRTS Reference ID 3766366)

[5] 7/30/15 Type A Meeting Minutes (Reference ID 3812611)

data are essential for FDA's review since there is very little in the literature regarding barium use in pediatrics. FDA acknowledged at the meeting that barium use in pediatric patients is declining and that the applicant would be relying on the opinions of medical experts as to what product(s) are being used in the pediatric population. FDA stated that the survey data would be reviewed as part of the E-Z-HD NDA and would be used to inform labeling (b) (4).

At the meeting, FDA also acknowledged the applicant had provided published literature and survey information to support approval of Readi-Cat 2/Smoothie for all pediatric age groups, so their iPSP should explain that they are pursuing approval of the product for all pediatric age groups and that they will not be requesting waivers or deferrals for pediatric assessments under PREA. On August 30, 2015, the applicant submitted a request to defer studies in all pediatric age groups for NDA 208143 in order to first obtain further evidence on the current clinical use and medical need for both Readi-Cat 2 suspensions in pediatric patients.

III. Clinical Pharmacology[6]

Barium sulfate is pharmacologically inert and demonstrates negligible absorption from the GI tract following either oral or rectal administration. Barium sulfate is excreted, unchanged, in stool at an excretion rate which is dependent on peristaltic activity. In normal subjects, oral barium is generally excreted within 24 hours and rectally administered barium is eliminated with evacuation of the enema.

Barium sulfate use is based on absorption of x-rays due to filling of the GI tract lumen or coating of the mucosal surface, after oral or rectal administration, or instillation into an indwelling enterostomy tube or catheter. E-Z-HD is typically given with sodium bicarbonate effervescent granules, which release carbon dioxide gas to obtain distension of the upper gastrointestinal tract and to enhance mucosal visualization. Co-administration of EZ-HD with sodium bicarbonate allows double contrast fluoroscopic evaluation to locate and outline normal structures, (b) (4)

IV. Pediatric Use Survey

The applicant agreed to conduct a survey among current users and medical experts of barium sulfate products to determine how or if these products are used in pediatric patients during CT and fluoroscopy examinations to inform their iPSP and product-specific pediatric assessment(s) for submission (b) (4) The applicant submitted the survey results to NDA 208036 on September 14, 2015.

DPMH Comment: This reviewer focused on the survey results as they apply to only NDAs 208036 and 208143 for E-Z-HD and Readi-Cat 2, respectively, since both NDAs are the focus of this DPMH consult request.

[6] 8/16/15 Medical Officer Review of NDA 208036 (Brenda Q. Ye; DARRTS Reference ID 3810025)

A. Survey Methodology

The applicant administered two surveys to two different groups of medical professionals based on the imaging studies being queried. One survey entitled, General Barium Survey, targeted responses from radiologists, CT/radiology technicians, or CT/radiology managers who perform abdominal and/or pelvic CT and/or fluoroscopy studies. The other survey entitled, Barium Swallow Survey, targeted responses only from speech pathologists who perform modified barium swallow (MBS) studies.

The applicant emailed the surveys to (b) (4) potential General Barium Survey respondents and to (b) (4) potential Barium Swallow Survey respondents who were identified from the applicant's sales contact list. The email provided a link to the electronic questionnaire. Potential respondents who had received the email but failed to take the survey were contacted by phone so a direct phone interview could be conducted using the same questions as those contained in the electronic questionnaire.

In each survey, potential respondents were first asked the following two qualifying questions:

1. In your practice, do you use barium sulfate [to perform CT and/or fluoroscopy studies for General Barium Survey] or [to evaluate the oral, pharyngeal, and upper esophageal phases of swallowing for the Barium Swallow Survey] in **pediatric patients**?

2. Are you familiar with protocols at your institution for performing [relevant studies] with barium in **pediatric patients**?

In both surveys, potential respondents were allowed to proceed if they responded yes to both questions. The respondents were classified as barium users if they responded yes to both qualifying questions or as non-barium users if they responded no to one of the qualifying questions.

The General Barium Survey was designed as a 10 minute web-based questionnaire and was divided into the following three sections:

1. Imaging modality (i.e. fluoroscopy, CT)

2. Gastrointestinal (GI) segment

   - Fluoroscopy: oral, pharyngeal, and upper esophageal phases of swallowing for MBS examinations; esophagus and upper GI tract; small bowel examinations; colon for barium enema examinations

   - CT of abdomen and pelvis

3. Name(s) of product(s) used according to the following pediatric age groups: (1) under 2 years; (2) 2 years to 12 years; (3) greater than 12 years. Dosage information in milliliters (mL) per dose was collected for each of these age groups as a free field.

The Barium Swallow Survey was designed as a 5 minute web-based questionnaire and asked respondents to provide the names(s) of product(s) used and dosage information for the same pediatric age groups as those collected in the General Barium Survey.

If a barium sulfate product was not used for a specific procedure or for imaging a certain segment of the GI tract, the respondent was asked to provide the alternative procedure (if any) that was routinely used at their practice. Demographic information and number of procedures performed with barium sulfate products at respondents' institutions or practices were also recorded.

B. Survey Results

The overall response rate for both surveys combined was 8.1% (480/5,937). Among the 480 total survey respondents, 48.3% (232/480) were barium users. Detailed dosing information was not provided in the study report. The applicant indicated that the reported dosing information was too limited and scanty to support a conclusion about the optimal dosing regimen.

1. General Barium Survey

The response rate to the initial email was (b) (4) but increased to (b) (4) when the remaining recipients were contacted directly by phone. The majority of respondents were technologists (114) followed by imaging directors/managers (27), radiologists (17), and speech language pathologists (10). The majority of respondents were affiliated with a community hospital (83) followed by an academic hospital (48) and a tertiary hospital (9). Among the 429 survey respondents, 45.9% (197/429) were barium users while 54.1% (232/429) were non-barium users.

DPMH Comment: Barium users most frequently reported using barium sulfate products for fluoroscopy studies of the esophagus and upper GI tract than the other imaging studies queried (see Table 1). Among the 128 respondents who reported barium use for fluoroscopy of the esophagus and UGI tract, 35.9% reported the use of E-Z-HD across all pediatric age groups (see Table 2). Reported use of E-Z-HD for fluoroscopy of the esophagus and UGI tract in this survey was comparable to the reported use of Readi-Cat 2 formulations for CT of the abdomen and pelvis.

Approximately 52.8% (75/142) of respondents who were classified as barium users stated that barium is used in their practice during CT exams in pediatric patients, and close to 40% of them reported the use of a Readi-Cat 2 formulation in pediatric patients of all ages (see Table 2).

Approximately 41.8% of the other respondents classified as barium users who indicated they do not use barium for CT exams (28/67) provided information about alternative diagnostic procedures, and almost all of them reported using water soluble contrast agents. Some of these respondents provided dosing information, reporting that 450 mL of the barium suspension is usually administered to patients' age 2 years to 12 years and 450 to 900 mL of the barium suspension is administered to patients' older than age 12 years.

Table 1. Pediatric barium sulfate use for the specified imaging among respondents to the General Barium Survey who were classified as barium users (N=197) and provided information about barium sulfate use for fluoroscopy of the esophagus and UGI tract (n=174); for fluoroscopy of the colon (n=145); for fluoroscopy of the small bowel (n=143); and for CT of the abdomen and pelvis (n=142).

Study Type Queried	N = 197 Barium Users
Fluoroscopy: Esophagus and Upper GI	73.5% (128/174)
Fluoroscopy: Small Bowel	56.6% (81/143)
Fluoroscopy: Colon	41.4% (60/145)
CT abdomen and pelvis	52.8% (75/142)

(Source: created by this reviewer)

Table 2. Proportion of respondents in the General Barium Survey classified as barium users (n=197) who reported using either E-Z-HD or Readi-Cat2 products for fluoroscopy and CT, respectively, in different pediatric age groups.

Study Type	No. E-Z-HD Users				
	Total	≤ 1 mo	< 2 yrs	2-12 yrs	> 12 yrs
Fluoroscopy: Esophagus and Upper GI	46	28	28	34	42
	No. Readi-Cat 2 Users				
CT abdomen and pelvis	31	20	21	24	26
	No. Readi-Cat 2 Smoothie Users				
CT abdomen and pelvis	28	17	17	20	22

(Source: Adapted from Tables D, E, F) *Total number of respondents who reported use of the barium product, across all age groups; mo = months; yrs = years

DPMH Comments:

Several aspects of the survey design were appropriate. First, the survey appears to be a non-probability, purposive sampling design[7] of radiologists, radiology technicians, and speech pathologists and, therefore, appropriately targeted healthcare professionals most likely to prescribe and use barium sulfate products for medical imaging. Second, the applicant's use of their sales contact list to identify potential survey respondents likely captured all current purchasers since the applicant is the sole provider of barium sulfate medical imaging products in the United States. Third, the two qualifying questions

[7] Braithwaite D, Emery J, de Lusignan S, et al. Using the Internet to Conduct Surveys of Health Professionals: A Valid Alternative? Family Practice 20: 545-551, 2003.

appropriately attempted to identify those users of barium sulfate medical imaging agents who would be most qualified to answer the survey questions.

The low survey response rate limits the generalizability of the results. The response rate to the initial email was only 9% but increased to 19.9% when the remaining recipients were contacted directly by phone. While physicians are a professional group with typically low survey response rates,[8] a survey response rate of 70% or higher is generally considered appropriate and desirable for external validity.[7,9]

Furthermore, the applicant did not provide any reasons to explain the low response rate in this survey. The length of time required to complete the survey was within the 13 minute completion time considered by some as the ideal length to obtain a good response rate,[9] so survey length should not have played a significant role. Multiple possible explanations for the low 9% initial response rate the initial email inquiry include the following:

- *Recipients thought the email was commercially-affiliated or was considered to be "spam".[9] Surveys sponsored by academic and governmental agencies have higher response rates than those from commercial entities.[9] One systematic review of web-based surveys of healthcare professionals identified 12 publications with response rates ranging from 9% to 94%.[7] This review also noted that respondents to electronic surveys are usually not representative of the general population of healthcare professionals even within a certain medical specialty.*
- *Recipients failed to receive the initial email due to an outdated contact list.*
- *No pre-notifications were sent to potential respondents prior to sending the initial email. Several meta-analyses of mail and web surveys have consistently concluded that the number of times potential respondents are contacted is one of the most important factors predicting response rates and that pre-notifications play a particularly critical role.[9]*
- *Lack of a financial incentive to respond.[10]*

Failure for a majority of potential respondents to participate in these surveys may have contributed to non-response bias.[8] The applicant must address this bias to determine if the small number who did respond is representative of the healthcare professionals most likely to use and prescribe barium sulfate products. This is key to determining whether or not the survey results can be generalized from the responders to the broader target population of healthcare professionals most likely to use barium sulfate products.[10]

[8] Cunningham CT, Quan H, Hemmelgarn B, et al. Exploring Physician Specialist Resposne Rates to Web-Based Surveys. BMC Medical Research Methodology 15: 32-40, 2015.

[9] Handbook of Survey Methodology for the Social Sciences. Edited by Lior Gideon; Springer New York, 2012.

Additional methodological limitations include the following:

- *The survey report did not provide annual sales distribution data for barium sulfate products to different institutional settings. This information is important to ensure that the institutional affiliations for those who responded to the survey are representative of healthcare settings with the greatest sales distribution of barium sulfate products. For instance, respondents were less commonly affiliated with academic hospitals than community hospitals but interpretation of these findings may differ if the majority of barium sulfate products are sold to academic hospitals.*
- *The applicant relied on their sales contact list to capture all purchasers of barium sulfate products, but if product purchasing occurs through a centralized distributor, then the number of purchasers may not accurately represent all those who actually use the product and/or conduct the imaging studies.*
- *The study report did not specify the distribution of institutional settings to which initial emails were sent. Even though the majority of respondents were affiliated with a community hospital, they may not have represented the majority of potential respondents who initially received the survey by email. Only 11.4% (49/429) of General Barium Survey respondents stated they practiced at a children's hospital.*

V. Conclusions

(b) (4)

The applicant submitted 505(b)(2) NDA submissions for E-Z-HD (NDA 208036) and Readi-Cat 2/Readi-Cat 2 Smoothie (NDA 2081432) in December 2014. E-Z-HD is a 98% barium sulfate suspension proposed for use in double contrast radiography of the UGI tract. Readi-Cat 2 and Readi-Cat 2 Smoothie are 2% barium sulfate suspensions proposed for CT of the abdomen (b) (4)

DMIP filed both NDAs without agreed upon iPSPs because of the need to review marketed unapproved drugs products but subsequently agreed the applicant could conduct a survey among current users and medical experts of barium sulfate products in pediatric patients to confirm how these products are used (b) (4)

[10] Burns KE, Duffett M, Kho M, et al. A Guide for the Design and Conduct of Self-Administered Surveys of Clinicians. Canadian Medical Association Journal 179(3): , 245-252, 2008.

The survey results were submitted under [redacted] (b) (4) (NDA 208036) on September 14, 2015. While the General Barium Survey appropriately targeted qualified healthcare professionals most likely to prescribe and use barium sulfate products for medical imaging in the United States, the inexplicably low survey response rate of only 19.9% limits the generalizability of the results. The reported use of E-Z-HD for fluoroscopy of the esophagus and UGI tract was comparable to the reported use of Readi-Cat 2 formulations for CT of the abdomen and pelvis. However, the absolute number of respondents who reported barium use for these imaging procedures was low due to the overall low survey response rate. The survey report lacked the following key information to determine whether or not the survey results can be generalized from the small number of responders to the broader target population of healthcare professionals most likely to use barium sulfate products:

- The applicant did not provide any reasons to explain why the response rate was so low in this survey and failed to address the potential impact of non-response bias on the survey results.
- Annual sales distribution data for barium sulfate products sold to different institutional settings represented in this survey was not provided to ensure that the institutional affiliations for those who responded to the survey are representative of healthcare settings with the greatest sales distribution of barium sulfate products.
- The study report did not specify the distribution of institutional settings to which initial emails were sent. Even though the majority of respondents were affiliated with a community hospital, they may not have represented the majority of potential respondents who initially received the survey by email. Less than 12% of respondents were affiliated with a children's hospital.

Detailed dosing information was not provided in the survey report. DPMH concurs with the applicant that the reported dosing information was too limited and scanty to support a conclusion about the optimal dosing regimen.

VI. Recommendations

DPMH previously agreed, in the absence of survey data, that a full pediatric waiver for E-Z-HD would be acceptable on the basis that studies in pediatric populations would be impossible or highly impracticable because of the low incidence of conditions that would require double-contract barium examination in pediatric patients.[3] The General Barium Survey results do not support this justification because they suggest that E-Z-HD is used for fluoroscopy of the esophagus and UGI tract in all pediatric age groups. Due to methodological limitations, the survey likely did not capture the full extent of pediatric use of these products.

The survey findings are in accordance with practice parameters published by the American College of Radiology (ACR) and the Society for Pediatric Radiology (SPR) which state that barium is the preferred contrast medium for most esophagrams and UGI examinations in pediatric patients.[11] The ACR and SPR further state that single-contrast studies are typically performed while double-contrast studies are seldom performed except to potentially help evaluate mucosal integrity in adolescents. The preferential use of single- versus double-contrast studies was not confirmed in the Barium Survey since the survey questionnaire did not ask respondents whether they use barium products to conduct single- versus double-contrast fluoroscopy examinations; this distinction is important because E-Z-HD is being proposed for use only in double-contrast examinations.

The survey results cannot be generalized to the broader target population of healthcare professionals most likely to use barium sulfate products with confidence without additional information about the reasons for the low survey response rate, characteristics of the non-responders, and barium sulfate products sales distribution data to the institutional settings queried. The survey results do not provide sufficient information to inform pediatric dosing of E-Z-HD and Readi-Cat 2 for the proposed indications.

DPMH recommends the following:

1. The applicant should clarify the number and percentage of respondents who reported using barium for fluoroscopy of the esophagus and UGI tract perform single- versus double-contrast examinations.

2. The survey report contains insufficient data to support a conclusion about the optimal dosing regimen for E-Z-HD and Readi-Cat 2/Readi-Cat 2 Smoothie.

3. The applicant should provide data from guidelines issued by radiological societies, textbooks, and peer-reviewed literature to justify the proposed dosing and to support the safety of E-Z-HD in pediatric patients for the proposed indication.

4. (b) (4)

[11] ACR-SPR Practice Parameter for the Performance of Contrast Esophagrams and Upper Gastrointestinal Examinations in Infants and Children; Revised 2015

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONA K KHURANA
11/23/2015

HARI C SACHS
11/23/2015
I agree with these recommendations.

LINDA L LEWIS
11/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 24th, 2015
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208036
Product Name and Strength:	E-Z-HD (Barium Sulfate) powder for suspension 98% (w/w)
Product Type:	Mullti- Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bracco Diagnostics Inc.
Submission Date:	January 8th, 2015
OSE RCM #:	2015-113
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Yelena Maslov, Pharm.D.

1 REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) requested that we review the E-Z-HD (Barium Sulfate) powder for Suspension 98% (w/w) current container and carton labels and proposed Prescribing Information for areas that may lead to medication error.

E-Z-HD has been in the US Market since 1980. However, the FDA has never approved this product. As a result, on January 8th, 2015 Bracco submitted an NDA for E-Z-HD (barium sulfate) powder for oral suspension 98% (w/w) and proposed proprietary name review for the product.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This review identified three post-market medication errors which included two reports of wrong route of administration (intravenous instead of oral) and one case of wrong drug use (Readi-Cat 2 instead of E-Z-HD) (See Appendix D.2). In terms of wrong route of administration error cases, accidental intravenous administration of the drug can lead to potentially fatal complications, which include systemic and pulmonary embolism, disseminated intravascular coagulation, septicemia and prolonged severe hypotension.

In addition, the packaging of E-Z-HD looks similar to other barium sulfate products currently in the market, which consequently has resulted in dispensing the incorrect product as evidenced by the post-marketing case of confusion between E-Z-HD and Ready-Cat2.

Given the potential for mix-ups and incorrect route of administration, we recommend some labeling updates for the product. Thus, we are providing our recommendations regarding label and labeling in Section 4.2

Additionally, we spoke to clinical team regarding the labeling concerns we had with the product related to the usage of percentages versus concentration in milligrams, the presence of the GI image on the display panel, and providing measuring markings on the label. Please refer to Appendix E for that discussion.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information:

1. Section 2 Dosage and Administration: We recommend the addition of statement: "E-Z-HD is for oral use" under this section.

4.2 RECOMMENDATIONS FOR THE BRACCO DIAGNOSTICS INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label:

1. We recommend adding route of administration to the primary display panel which would state: "For Oral Use Only" due to wrong route of administration errors that have occurred with this drug (i.e., intravenous administration instead of oral), which could potentially inflict great harm.

2. We recommend changing the background color of the label as the label looks very similar to other barium sulfate products, such as Volumen and Readi-Cat 2 (Vanilla Smoothie), which may result in selection of the wrong product. In fact, post-marketing experience demonstrated that E-Z HD was confused with Readi-Cat 2.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for E-Z-HD that Bracco Diagnostics submitted on January 8th, 2015.

Table 2. Relevant Product Information for E-Z-HD	
Initial Approval Date	N/A
Active Ingredient	Barium Sulfate
Indication	For use in double-contrast radiographic examination of the esophagus, stomach, and duodenum (b) (4)
Route of Administration	Oral
Dosage Form	Powder for suspension
Strength	98%
Dose and Frequency	65-135 mL
How Supplied	In a single use HDPE plastic bottle containing 340g of barium sulfate powder for oral suspension
Storage	Room Temperature 20 to 25 degrees Celsius (68 to 77 deg F)
Container Closure	HDPE plastic bottle

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 15th, 2015, we searched the L:drive and AIMS using the terms, Barium Sulfate to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any relevant reviews.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

On June 23rd, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care, Community Care, and Nursing
Search Strategy and Terms	Match Any of the Words: E-Z-HD

C.2 Results:

Our search did not identify any reports.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 19th, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[1]

Table 3: FAERS Search Strategy	
Date Range	**January 01, 1980 or March 19th, 2015**
Product	**Barium Sulfate**
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT]

D.2 Results

Our search identified 17 cases, of which 3 described errors relevant for this review.

Two cases (n=2) reported incorrect route of administration where E-Z-HD was given through IV line. In one case, it was reported that the patient was scheduled for small bowel exam, and the technician mistakenly injected with E-Z-HD suspension through a Groshong Catheter which was positioned in the right atrium of the heart (approximately 40 cc's of barium was injected). As a result, patient was transferred to intensive care. The report noted that the patient had directed the technician to administer the drug to her IV line, and the error was attributed to miscommunication between the patient and the technician.

In the second case, the radiology department dispensed oral contrast for IV contrast. A nurse prepared a syringe containing the oral contrast and injected it into the dialysis catheter. It was reported that the bottle contains no warning that it is for oral or enteral use only. The patient suffered extravasation of the material into the abdomen and prolonged hospitalization. A full root cause analysis was done on the event. Radiology stated that they were not aware that the enteral contrast does require a prescription. Furthermore, it was stated that Radiology have not like the labeling on the number of other manufacturer packages of barium sulfate suspension which they have previously used.

One case reported (n=1) that wrong product dispensed, patient received E-Z-HD instead of Readi-Cat Smoothie (Barium Sulfate) oral suspension 2% w/v. It was reported that a male in-

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

patient (already being hospitalized) was scheduled to have a CT with Readi-Cat 2 Berry Smoothie Barium Sulfate Suspension (2.1% w/v, 2.0% wlw) on (b) (6). Instead, the floor was supplied with the wrong barium product and the patient was given E-Z-HD Barium Sulfate for Suspension (98% w/w). The patient drank 1 bottle of the E-Z-HD at midnight on (b) (6) and another bottle at 6am the morning of exam on (b) (6). The exam was never completed. The facility became aware and administered enema and Go-Lytely and patient was able to eliminate the barium sulfate and did not need surgery.

We excluded the remainder of 14 cases because they described other barium sulfate products and not specific to E-Z-HD.

D.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case Number	Manufacturer's No	Country	Year
3115920	2411512-1998-00001	USA	1998
3864603	N/A	USA	2002
6216978	2411512-2006-00004	USA	2006

D.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains inormation on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX E. Communication between DMEPA and DMIP in regards to labeling.

From: Rahimi, Leeza
Sent: Friday, May 08, 2015 12:08 PM
To: Orzach, Harris; Fejka, Richard
Cc: Todd, Nushin F
Subject: EZ-HD and Readi-Cat 2 NDA 208036 and NDA 208143

Hello Dr. Orzach,

I am DMEPA's safety evaluator for the barium sulfate products. We had some questions concerning labeling, and we would appreciate any feedback on the following items:

1. Do you ever rely on the percentages (i.e.98% for EZ-HD and 2% for Readi-Cat) or do you think concentration of mg/ml or weight expressed in mg would be better?

2. The pictures of GI system on the bottles; are they helpful for identifying the area of use? We want to get your opinion if they really accurately represent the areas which product is supposed to be used in.

3. Lastly, do you find it helpful if the bottles have markings for measurements? Since the dosing is between 65mL-135 mL for E-Z-HD and 450-900mL for Readi-Cat 2, how are the doses measured? In the pharmacy it is dispensed as the entire bottle, but we wanted to get your input if it would be easier to have some type of markings to facilitate administration?

Thank you in advance.

Sincerely,

Leeza

From: Orzach, Harris
Sent: Tuesday, May 12, 2015 2:27 PM
To: Rahimi, Leeza
Subject: RE: EZ-HD and Readi-Cat 2 NDA 208036 and NDA 208143

Hi Leeza,

Sorry about the delay. In answer to your questions:

1. We customarily rely on percentages. E-Z-HD comes as powder- 98%w/w, in a (b) (4) container. It is reconstituted by adding 65 ml (b) (4) water, yielding 135 ml barium sulfate suspension, (b) (4). Ready-CAT2 comes as a premade suspension, 2.0% w/v, 450 ml per container.
2. At this time, I only have access to the E-Z-HD label. It highlights the esophagus, stomach and duodenum, which are the appropriate areas of usage.
3. To reconstitute the E-Z-HD, one adds 65 ml water to the barium sulfate powder in the bottle. Having a marking on the container might simplify this, but is not absolutely necessary. The Ready-CAT2 comes as a liquid barium sulfate suspension, 450 ml/container, ready to use.

I hope this satisfactorily answers your questions. Please let me know if more information is needed. Thank you.

Harris

From: Rahimi, Leeza
Sent: Tuesday, May 12, 2015 4:32 PM
To: Orzach, Harris
Subject: RE: EZ-HD and Readi-Cat 2 NDA 208036 and NDA 208143

Hi Harris,

Thank you so much for the response. We will take the answers into consideration when addressing the labeling recommendations.

Just to clarify question number 3, per your knowledge and experience do you know how does a healthcare provider measure the exact amount of E-Z-HD after reconstitution? Since not all the patients will receive the entire bottle (135mL), is it measured in a separate measuring device and then given to the patient?

Thank you.

Leeza

Leeza,

We encourage full size adults to drink the entire 135 ml, if they can. But it is not an exact science. We watch the stomach fluoroscopically, and if it is 1/3 to ½ full, that is enough for a good double contrast study. If the stomach empties more rapidly, they may have to drink more of the 135 ml. Sometimes they will drink what we initially believe is sufficient, but we may have to give more later in the study, to get the views we need, or demonstrate the pathology that we see.

Every UGI ends with single contrast esophagram using liquid E-Z [redacted] (b) (4) (60%w/v)(usually 1/3 to ½ bottle,) and some patients will drink an additional bottle of E-Z [redacted] (b) (4) if they require a small bowel follow-through. This additional barium can also be used to further evaluate the stomach, if necessary.

I hope this answers your questions. Thank you.

Harris

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEEZA RAHIMI
07/06/2015

YELENA L MASLOV
07/06/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # **208036** BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: **E-Z-HD** Established/Proper Name: **barium sulfate for suspension, 98% (w/w)** Dosage Form: **powder for suspension** Strengths: **98%w/w**		
Applicant: **Bracco Diagnostics Inc.** Agent for Applicant (if applicable):		
Date of Application: **12/11/2014** Date of Receipt: **12/11/2014** Date clock started after UN:		
PDUFA/BsUFA Goal Date: **December 11, 2015**	Action Goal Date (if different):	
Filing Date: **February 9, 2015**	Date of Filing Meeting: **January 21, 2015**	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☒ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): **For use in double-contrast radiographic examinations of the esophagus, stomach and duodenum** (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): **PIND115090**	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☐	☒		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐	X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 11/14/2014, 11/21/14 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐	X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 21, 2015

BACKGROUND: On December 11, 2014, Bracco Diagnostics Inc., submitted NDA 208-036 (Barium Sulfate Suspension 98%-EZ-HD) for use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum (b) (4) [redacted]

With this application, the applicant is requesting for full waiver of pediatric studies.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frank Lutterodt	Yes
	CPMS/TL:	Kyong Kang	Yes
Cross-Discipline Team Leader (CDTL)	Alexander Gorovets		Y
Division Director/Deputy	Libero Marzella		Y
Office Director/Deputy	Charles Ganley		Y
Clinical	Reviewer:	Harris Orzach	Y
	TL:	Libero Marzella	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y

Biostatistics	Reviewer:	Satish Misra	Y
	TL:	Jyoti Zalkikar	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ronald Honchel	Yes
	TL:	Adebayo Laniyonu	
Statistics (carcinogenicity)	Reviewer:	N/A	N
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Anne-Marie Russell Matin Haber	Y
	TL:	Eldon Leutzinger	Y
Biopharmaceutics	Reviewer	N/A	
	TL:		
Quality Microbiology	Reviewer:	Jessica Cole	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Nushin Todd—ADL Jagjit Grewal-ADRA Charles Ganley- Office Director		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain: M-010 in Module 3.3.P.5.2 was provided in French. Request will be in Day 74 letter	☐ YES ☒ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☐ YES

If no, explain:	☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Charles Ganley- Office Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: This product is a Type 7 NDA not in the "Program"

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK A LUTTERODT
02/10/2015