CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208036Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 20, 2015
From	Nushin Todd, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208036
Applicant	Bracco Diagnostics
Date of Submission	December 11, 2014
PDUFA Goal Date	January 11, 2016 (after major amendment extension)
Proprietary Name / Established (USAN) names	E-Z-HD / barium sulfate
Dosage forms / Strength	Powder for oral suspension / 98% (w/w)
Proposed Indication(s)	Double-contrast radiographic examination of the abdomen (b) (4)
Recommendation	Approval

1. Introduction

The applicant, Bracco Diagnostics, submitted a new drug application (NDA) to support the marketing of E-Z-HD, barium sulfate powder for suspension, for use in double contrast radiography of the upper gastrointestinal (GI) tract. This NDA is a 505(b)(2) submission that relies on literature citations, marketing surveillance, and publically available information on barium sulfate products; no preclinical or clinical studies were conducted by the applicant specific to this application. This is the first of several applications planned for submission by Bracco Diagnostics. In discussions between the applicant and the FDA, it was agreed this NDA will serve (b) (4) for subsequent submissions of barium sulfate products. As such, information necessary for approval of upcoming barium sulfate products would be referenced to the information provided in this submission. Review of this NDA, therefore, will include not only assessing E-Z-HD for approval but also on evaluating the clinical safety, efficacy and utility of barium sulfate products in general as a radiographic contrast agent in visualizing the GI tract. The findings and determinations from this NDA review will be cross-referenced in subsequent reviews of barium sulfate products planned to be submitted by the applicant. The disciplines and reviewers involved with evaluating this NDA are provided in Table 1.

Table 1 FDA Disciplines and Reviewers Involved in the Evaluation of NDA 208036

Discipline	Reviewer	Team Leader
Chemistry, Manufacturing and Controls Drug Product Drug Substance Process Facility Biopharmaceutics Microbiology	Dr. Anne Marie Russell Dr. Martin Haber Dr. Li Hsieh Dr. Thuy Nguyen Dr. Assadollah Noory Dr. Jessica Cole	Dr. Eldon Leutzinger, Supervisory Dr. Danae Christodoulou Dr. Donna Christner Dr. Nallaperumal Chidambaram Dr. Zhihao Qiu Dr. John Duan Dr. Stephen Langille
Nonclinical Pharmacology/Toxicology	Dr. Ronald Honchel	Dr. Adebayo Laniyonu
Clinical Pharmacology/Biopharmaceutics	Dr. John Christy	Dr. Gene Williams
Clinical	Dr. Brenda Ye	Dr. Louis Marzella
Statistics	Dr. Satish Misra	Drs. Tom Gwise and Jyoti Zalkikar
Pediatric and Maternal Health	Dr. Mona Khurana	Dr. Hari Sachs
Labeling Division of Medication Error Prevention and Analysis Labeling Development Team Prescribing Information	Dr. Leeza Rahimi Dr. Ann Marie Trentacosti and Jeanine Best, PNP	Dr. Yelena Maslov Dr. Eric Brodsky Dr. Nushin Todd

2. Background

Barium sulfate, in various formulations, has been used to opacify the GI tract since the early 1900s. However, all barium sulfate products used to date as diagnostic imaging agents have been marketed as unapproved drugs.

The applicant has been manufacturing and distributing barium sulfate products since 2008 and is the sole supplier of these products in the US. (b) (4)

Information to support approval of this submission was provided by the applicant from the following sources: Guidelines issued by the American College of Radiology (ACR); Guidelines on the safety of contrast agents issued by the European Society of Urogenital Radiology (ESUR); radiology textbooks; published papers and review articles retrieved from the literature; and post-marketing surveillance database worldwide between 2009 and 2014.

During the review process, the applicant submitted a survey conducted in the medical community about the use of barium sulfate products in pediatric patients. The submitted survey was classified as a major amendment by the FDA and therefore extended the action date for determining approval of the NDA by three months, to January 11, 2016.

(b) (4)

Product Names	Dose Form	Route of Administration	Type of Examination and Target Segment of GI
Radiography/Fluoroscopy (Conventional X-ray)			
E-Z-HD	Powder for suspension	Oral	Double-contrast radiographic examinations of the esophagus, stomach and duodenum
Varibar Thin Liquid	Powder for suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharnyx / Swallowing studies
Varibar Nectar	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharnyx / Swallowing studies
Varibar Thin Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharnyx / Swallowing studies
Varibar Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharnyx / Swallowing studies
Varibar Pudding	Paste	Oral	Radiographic examinations of the esophagus, pharynx and hypopharnyx / Swallowing studies
Liquid E-Z-Paque	Suspension	Oral	• Single-contrast radiographic examinations of the stomach • Small bowel follow-through after single-contrast or double-contrast upper GI study
E-Z-Paste	Paste	Oral	Single-contrast radiographic examinations of the esophagus, pharynx, hypopharynx and for cardiac series
Entero Vu 24%	Suspension	Oral	For use in small bowel radiographic examinations
Liquid Polibar Plus	Suspension	Oral	Radiographic examinations of .esophagus (undiluted for double contrast), cardiac series, stomach (single- and double-contrast) and small bowel series.
Liquid Polibar Plus (E-Z-Dose)	Suspension	Rectal	Single- and double-contrast radiographic examinations of the colon
E-Z-Disk	Tablet	Oral	Radiographic examinations of the esophagus for detection of esophageal strictures
E-Z-Paque	Powder for suspension	Oral	Single-contrast radiographic examinations of the esophagus, stomach, duodenum and small bowel
CT Exams – Opacification of GI Tract at CT Imaging			
E-Z-Cat Dry	Powder for suspension	Oral	CT examinations of the abdomen
Readi-CAT2	Suspension	Oral	CT examinations of the abdomen
Readi-CAT2 Smoothies: **a. Berry** **b. Banana** **c. Creamy Vanilla** **d. Mochaccino**	Suspension	Oral	CT examinations of the abdomen
Tagitol V	Suspension	Oral	For use in opacifying residual stool in the colon at CTC
GI: gastrointestinal; CT: computed tomography; CTC: CT colonography.			

(Table 2, submitted by applicant to NDA 208036)

3. CMC

A thorough review of the submission from a Chemistry, Manufacturing, and Controls (CMC) perspective posed to be challenging due to the absence of a reference listed drug (RLD) and the literature-based approach of the application. Because of the lack of a RLD, it was not possible to evaluate the quality of the proposed product to determine comparability and provide assurance that the product would perform as labeled. To circumvent this obstacle, the CMC reviewers examined data of barium sulfate products on the market at the time that specific clinical studies were conducted. In addition, the reviewers examined information on the products use as formulated in the NDA.

Product Quality

Quality standards for barium sulfate products were assessed through the quality of the ingredients, batch history, and stability.

Barium is (b) (4) in the production of the final drug product, E-Z-HD barium sulfate for suspension.

As noted above, initial obstacles were encountered in assessing the product quality of E-Z-HD because of the absence of a RLD and lack of clinical studies. However, barium sulfate products similar to E-Z-HD were used in the 1970's; literature reports of these older products were requested. The applicant submitted 9 studies from referenced literature spanning from 1976 to 2005. Using suitable quality standards framework that included formulation, particle size, and viscosity, the proposed commercial product, E-Z-HD, was compared with the products used in the referenced studies. Based on the results of these comparisons, the CMC reviewers concluded that E-Z-HD is comparable with similar products marketed decades earlier.

Review of drug substance quality revealed the potential for trace metal impurities. (b) (4) Twelve elements which included (b) (4) were identified as possible impurities. The applicant proposed impurity limits and provided an expert opinion toxicology report to support the safety of proposed limits. The potential risks for trace metal impurities were assessed by the CMC reviewers and determined to be minor and acceptable.

Overall, CMC reviewers found the purity and quality of barium sulfate drug substance derived from (b) (4) to be satisfactory for use in the manufacture of barium sulfate products such as E-Z-HD. No deficiencies were found in the purification, final preparation or packaging processes.

Quality standards for the inactive ingredients by USP specifications along with certificates of analysis were provided by the applicant and deemed acceptable. Additionally, review of all flavorings in the barium sulfate products, provided in DMFs, revealed no issues for quality.

Stability data initially submitted by the applicant was found to be for batches not packaged in the proposed NDA configuration. The applicant provided additional stability data during the NDA review. Based on the additional stability information, a two year expiration date was given for E-Z-HD, stored at 25 degrees centigrade. The applicant has provided a stability protocol, to be conducted post-approval, to extend the expiration date. CMC reviewers deemed the protocol acceptable.

Data for microbial limits at release and on stability for E-Z-HD were also reviewed and found to be acceptable.

Facilities Review

(b) (4) sub-contracts part of their release testing and all the stability testing to E-Z-EM located in Quebec, Canada. E-Z-EM is a fully owned subsidiary of the applicant. An inspection of both facilities, (b) (4) and E-Z-EM, was conducted in (b) (4) . No good manufacturing practices (GMP) deficiencies were identified in either facility.

From the CMC reviews, it was determined that the manufacturing process yields a product that is consistent and reproducible within the established product specifications, as well as current good manufacturing practices (cGMP) requirements. There are no unresolved CMC issues. I concur with the conclusions of the CMC reviewers.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team consisted of Dr. Ronald Honchel, reviewer, and Dr. Adebayo Laniyonu, team leader. Dr. Honchel's report, with concurrence from Dr. Laniyonu, was based on review of published literature for the barium sulfate containing products that is marketed by the applicant.

One published study revealed the LD50 of intragastrically administered barium sulfate is calculated to be 364 g/kg in young male rats. The cause of death was stomach rupture. No other toxicology, carcinogenicity, or reproductive toxicology data were available for review.

In his review, Dr. Honchel notes that barium sulfate drug substance contains a number of impurities. CMC reviewers investigated the impurities and determined they are in trace amounts and within acceptable limits of the manufacturing process. Please refer to the previous section for further discussion on the matter.

Dr. Honchel points out that while there is nonclinical and clinical evidence to support the safety of the proposed use of barium sulfate plus the impurities present in E-Z-HD, there is no data on the effect the impurities present in E-ZH-HD may have on pregnancy, carcinogenesis, mutagenesis, and fertility. However, it should be noted that, similar to radioactive diagnostic agents, nonclinical reproductive toxicology studies have not been conducted for barium sulfate products since their use is not recommended during pregnancy given the risks of radiation exposure to the fetus.

The nonclinical review team could not recommend approval of the NDA from a discipline perspective due to lack of nonclinical data. However, they acknowledge the extensive clinical experience with barium sulfate worldwide over the past century and defer to the clinical team's assessment of barium sulfate for approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer for this application was Dr. Christy John. In his review, Dr. John acknowledges that no clinical pharmacology studies were conducted by the applicant

and that dosing, safety and efficacy of the product are based on referenced literature. Essential clinical pharmacology findings are highlighted below.

Absorption, Distribution, Metabolism and Elimination
E-Z-HD is a barium sulfate powder for oral suspension, 98% w/w. Reconstitution with 65 mL of water yields approximately 145 mL of a 23 (b) (4)% w/v oral suspension (2.3 (b) (4) grams barium sulfate per mL). The recommended dose is 65-135 mL oral suspension.

Barium sulfate is biologically insoluble and inert. The systemic absorption of barium sulfate from the GI tract is negligible after oral or rectal administration, or after instillation into an indwelling enterostomy tube or catheter. Barium sulfate is excreted, unchanged, in stool at an excretion rate which is dependent on peristaltic activity. Oral barium is generally excreted within 24 hours. Rectally administered barium is eliminated with evacuation of the enema.

The timeframe for barium sulfate to adequately opacify a segment of the GI tract varies according the route of administration, concentration, and viscosity of the administered barium suspension. Opacification of the upper GI tract occurs almost immediately after oral barium sulfate suspension whereas opacification of the small bowel occurs between 15 and 90 minutes post oral administration. Optimal opacification of the colon after barium enema administration is variable, depending on patient positioning, hydrostatic pressure and rate of barium administration.

Intrinsic Factors and Drug-Drug Interactions
Because barium sulfate is not absorbed and is biologically inert, no dosage adjustments are necessary for specific patient populations. Additionally, transporter-related interactions are not expected and there are no known interactions with other medicinal products.

Dr. John has determined NDA 208036 acceptable from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language. Dr. John's recommendations are supported by his team leader, Dr. Gene Williams. I concur with their findings.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical - Efficacy

E-Z-HD (NDA # 208143) is a 505(b)(2) application based on literature review. Under this NDA, the applicant has submitted the clinical data to evaluate the safety and efficacy of all barium sulfate drug products for use as contrast agents in various radiologic procedures for the opacification of the GI tract. Subsequent submissions of barium sulfate drugs will rely on this application for the repository of information needed for review. This NDA (b) (4) for all barium sulfate drug products that are submitted by the applicant.

A literature search of the PubMed database to support the efficacy of barium sulfate for diagnostic imaging procedures of the GI tract was conducted by the applicant. The search was limited to clinical articles in English from 1994 to 2014. Overall, the applicant focused the efficacy review on 48 publications specific to barium sulfate. These papers were categorized based on structural delineation of the GI tract by region (e.g., upper GI tract, small bowel examination, barium enema, etc.,) as well as by adult and pediatric populations.

The clinical reviewer, Dr. Brenda Ye, focused her efficacy review on published studies that: were prospective; evaluated performance characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) of barium sulfate and; used histopathology and/or endoscopy or surgery as the standard of truth.

Dr. Ye substantiated the efficacy of barium sulfate for at least one diagnostic use per region of the GI tract. Her findings are applicable to other diagnostic indications for barium sulfate based on similar mechanism of action. The citations were categorized based on the following regional indications for barium sulfate:

Esophagram and upper gastrointestinal series

(b) (4)

Modified barium swallow

Opacification of the GI tract in CT of the abdomen/pelvis

(b) (4)

Dr.Ye reviewed between 1 to 5 articles in depth for each of the above regional uses of barium sulfate products. For example, two publications were identified and assessed by Dr. Ye as providing literature evidence to support the efficacy of barium sulfate in double-contrast study of the esophagus and upper GI tract.

The statistical reviewer, Dr. Satish Misra, evaluated 5 citations specific to E-Z-HD and 1 citation for Readi-Cat 2 barium sulfate products. Dr. Misra conducted meta-analysis to supplement the sensitivity and specificity estimates reported in the publications. The studies reviewed by Dr. Misra, individually and collectively supported the clinical efficacy of E-Z-HD. Additionally, Dr. Misra has noted that quantitative data for Readi-Cat 2, albeit limited, was in the right direction in support of its indication.

Both, Drs. Ye and Misra, confirm evidence of diagnostic performance of barium sulfate in literature citations in support of barium sulfate for visualization of the GI tract. Please refer to their reviews for details of their assessments.

The review of efficacy through literature citations conducted by Drs. Ye and Misra were inherently limited. Issues with statistical analyses, study design, and verification of summary data at the patient level in the citations were contributing factors. Despite these limitations and the lack of adequate prospective trials specifically assessing efficacy of barium sulfate, there is, nonetheless, an abundance of evidence from over 100 years of its use worldwide in firmly establishing the clinical utility of barium sulfate for the visualization of the GI tract.

8. Safety

The safety of barium sulfate products has been well established during the more than 100 years of clinical use. The assessment of the safety of barium sulfate products was conducted by Dr. Brenda Ye. She reviewed safety information from published reports, practice guidelines, and marketing surveillance reports.

Practice guidelines describe the following common, non-serious, adverse reactions associated with barium sulfate: nausea, vomiting, abdominal discomfort, vasovagal reactions (attributed to viscous distension), diarrhea, and/diarrhea. Serious adverse reactions include: aspiration of orally administered barium, intestinal perforation and hypersensitivity reactions. The etiology of hypersensitivity reactions is postulated to be due to the excipients in the barium sulfate preparations. Although these excipients are used in a variety of food products and appear in the FDA list of products generally regarded as safe (GRAS), they may represent a potential source for hypersensitivity reactions during GI examinations.

Review of postmarketing safety surveillance information from January 2009 through July 2014 was provided by the applicant and reviewed by Dr. Ye. From approximately (b) (4) patients who received barium sulfate during this period, 308 adverse cases were reported as related to barium administration. There were 50 serious adverse events reported with the most common being: aspiration (n=14); barium impaction (n=4); and dyspnea (n=4).

The safety profile of barium sulfate preparations is similar in pediatric patients and adults. Common adverse events in pediatric patients include nausea, vomiting, abdominal discomfort, constipation, diarrhea and colonic retention of barium. Severe events, similar to adults, include perforation of the GI tract, aspiration of orally administered barium, and hypersensitivity reactions.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

The applicant did not submit an initial pediatric study plan (iPSP) prior to submission of this NDA as required by the Pediatric Research Equity Act (PREA) since the barium sulfate products are considered new active ingredients. The Division of Medical Imaging Products (DMIP) filed the application without an iPSP because of the need to review marketed but unapproved drug products. Subsequently, DMIP agreed the applicant conduct 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 an iPSP. (b) (4)

The pediatric survey data revealed that, in general, barium sulfate products are used in all pediatric age groups. There is variability regarding specific pediatric age groups for some

barium sulfate products. The survey, however, was limited due to the low number of responders and insufficient data to support optimal pediatric dosing.

Dr. Mona Khurana, from the Division of Pediatric and Maternal Health, and the clinical reviewer, Dr. Brenda Ye, reviewed the survey data. They also reviewed published literature, safety data, and practice guidelines from radiological societies regarding the clinical utility of barium sulfate in pediatric populations. The safety profile of barium sulfate products is well established and similar among adult and pediatric patients. Drs. Khurana and Ye concluded that limitations of use of barium sulfate products are not due to the drug, but rather to procedural considerations (e.g., radiation dose, need for patient cooperation, etc.,) in the younger pediatric age groups. For E-Z-HD, the reviewers determined that other than adolescents, there is limited applicability of double-contrast examinations in the pediatric population. Therefore, it is recommended that the indication for E-Z-HD be for adult and adolescent patients. Other barium sulfate products will be similarly assessed in subsequent applications.

The Pediatric Review Committee (PeRC) discussed the PREA requirements for the submitted barium sulfate products. PeRC agreed with DMIP's determination of including pediatric patients in the labeling of barium sulfate products based on the pediatric use survey, published literature and safety data. I concur with the determinations of the pediatric reviewers and PeRC.

11. Other Relevant Regulatory Issues

Not applicable

12. Labeling

Major revisions were made to the labeling of the barium sulfate products (E-Z-HD and Readi-Cat 2) submitted by the applicant. The Labeling Development Team (Jeanine Best, PNP, and Drs. Anne Marie Trentacosti and Eric Brodsky) and I revised labeling to conform to the current Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) requirements for labeling. Other major revisions included the incorporation of pediatric patients in the Prescribing Information (PI). The applicant provided pediatric dosing information for E-Z-HD labeling prior to the PDUFA deadline. Final labeling edits were made by me and the LDT. There was concurrence from all disciplines involved in the review of barium sulfate products regarding the edits to the labeling.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval

Risk Benefit Assessment

The safety and clinical utility of barium sulfate products as contrast agents in the visualization of the GI tract have been well established from more than 100 years of use worldwide. Based on the totality of information from marketing data on estimated exposures of approximately (b) (4) patients from 2009 to 2014; review of pediatric use; and literature-based review of the safety and efficacy of barium sulfate, it recommended that E-Z-HD specifically, and barium sulfate products in general, be approved. This recommendation was derived independently from all reviewers involved in evaluating the application.

The well characterized safety profile of barium sulfate products is similar between adult and pediatric patients. Serious adverse reactions are not common and are usually related to complications from the barium administration procedure. Hypersensitivity reactions from barium sulfate or excipients, which can be serious, are also uncommon.

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/s/

NUSHIN F TODD
01/04/2016