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RESEARCH**

*APPLICATION NUMBER:*

**208143Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	January 8, 2015
<b>From</b>	Nushin Todd, MD, PhD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	208143
<b>Applicant</b>	Bracco Diagnostics
<b>Date of Submission</b>	December 18, 2014
<b>PDUFA Goal Date</b>	January 18, 2016
<b>Proprietary Name / Established (USAN) names</b>	READI-CAT 2 and READI-CAT 2 SMOOTHIES / Barium sulfate
<b>Dosage forms / Strength</b>	Oral suspension / 2% (w/v)
<b>Proposed Indication(s)</b>	For use in computed tomography (CT) of the abdomen to help visualize the gastrointestinal tract in adult and pediatric patients
<b>Recommended:</b>	Approval

## 1. Introduction

The applicant, Bracco Diagnostics, has submitted the second <sup>(b) (4)</sup> new drug applications (NDAs) to support the marketing of their barium sulfate products. The current submission, NDA 208143, is for READI-CAT2 and READI-CAT2 SMOOTHIES. These are oral barium sulfate suspensions indicated for use in computed tomography (CT) of the abdomen to help opacify and delineate the gastrointestinal (GI) tract in adult and pediatric patients. READI-CAT2 and READI-CAT2 SMOOTHIE products are very similar in composition, except that READI-CAT2 SMOOTHIES are provided in four flavors (banana, berry, vanilla, and coffee). 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. Information needed for review of READI-CAT2 products has been provided by Bracco under their first NDA application (NDA 208036) for E-Z-HD, barium sulfate powder for suspension, for use in double contrast radiography of the upper gastrointestinal (GI) tract. In discussions between the applicant and the FDA, it was agreed the NDA for E-Z-HD (NDA 208036) will serve <sup>(b) (4)</sup> for subsequent submissions of barium sulfate products. Therefore, review of clinical safety, efficacy and utility of READI-CAT2 products will cross-reference findings for barium sulfate products noted in the E-Z-HD application. The reader is advised to refer to the reviews of E-Z-HD for details. The disciplines and reviewers involved with evaluating this NDA are the same as for E-Z-HD and are listed in Table 1.

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

<b>Discipline</b>	<b>Reviewer</b>	<b>Team Leader</b>
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 Lanionu
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.

(b) (4)

Product Names	Dose Form	Route of Administration	Type of Examination and Target Segment of GI
<i>Radiography/Fluoroscopy (Conventional X-ray)</i>			
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 hypopharynx / Swallowing studies
Varibar Nectar	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Thin Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Pudding	Paste	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Liquid E-Z-Paque	Suspension	Oral	<ul style="list-style-type: none"> <li>Single-contrast radiographic examinations of the stomach</li> <li>Small bowel follow-through after single-contrast or double-contrast upper GI study</li> </ul>
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
<i>CT Exams – Opacification of GI Tract at CT Imaging</i>			
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/Device

All READI-CAT2 products have a barium sulfate composition of 2 grams per 100 mL of solution. READI-CAT2 products contain: (b)(4) pharmaceutical grade barium sulfate, viscosity enhancing excipients, (b)(4).

READI-CAT2 products are white, low viscosity, flavored barium suspensions presented as a single-use 450 mL fill in a (b)(4) mL plastic bottle.

#### Product Quality

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

Review of drug substance quality revealed the potential for trace metal impurities. Using an inductively coupled plasma-optical emission spectroscopy (ICP-OES) method, the applicant conducted monitoring of trace metals in the (b)(4) lots in 2014. 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 the READI-CAT2 products. 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.

### **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 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**

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 in the urine 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.

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.

The clinical pharmacology review team determined NDA 208143 acceptable from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language. I concur with their findings.

## **6. Clinical Microbiology**

Not applicable

## **7. Clinical/Statistical - Efficacy**

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 and statistical review teams evaluated the relevant literature for efficacy of barium sulfate for visualization of the GI tract. Both teams independently confirmed the evidence of diagnostic performance of barium sulfate in support of barium sulfate in the delineation 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 conducted a survey among current users and medical experts of barium sulfate products in pediatric patients to confirm how these products are used. The pediatric survey data revealed that, in general, barium sulfate products are used in all pediatric age groups. There is variability, however, regarding specific pediatric age groups for some barium sulfate products. For READI-CAT2 products, the survey results suggested they are used in all pediatric age groups. 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.

READI-CAT has been available for years and dosing in pediatric patients varies among centers conducting the imaging studies. Given the limited data in the literature to support specific dosing for pediatric patients, it was determined that dosing recommendations in

labeling will be to adjust the READI-CAT2 dose relative to the GI volume in patients less than 12 years of age.

## 11. Other Relevant Regulatory Issues

Not applicable

## 12. Labeling

Major revisions were made to the labeling of the Read-Cat 2 products 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 of all ages in the Prescribing Information (PI). 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 is recommended that Read-Cat 2 products 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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01/15/2016