

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208143Orig1s000**

**OFFICE DIRECTOR MEMO**

**Office Director Decisional Memo**

<b>Date</b>	January 16, 2015
<b>From</b>	Charles J. Ganley, M.D. (Director ODEIV)
<b>Subject</b>	Office Director Decisional Memo
<b>NDA #</b>	NDA # 208143
<b>Supplement #</b>	
<b>Applicant Name</b>	Bracco Diagnostics Inc.
<b>Date of Submission</b>	December 11, 2014
<b>PDUFA Goal Date</b>	January 11, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Readi-Cat 2 (barium sulfate 2 g/100ml suspension); Readi-Cat 2 Smoothie (barium sulfate 2 g/100ml suspension)
<b>Dosage Forms / Strength</b>	2% w/v suspension
<b>Indication(s)</b>	... for use in computed tomography(CT) of the abdomen  (b) (4)
<b>Action:</b>	Approval
<b>Approved Indication(s)/Populations (if applicable)</b>	Adults and all pediatric age groups

<b>Material Reviewed/Consulted</b> OND Action Package, including:	<b>Names of discipline reviewers</b> (Entire list including team leaders is included in the CDTL)
<b>Medical Officer Review</b>	Brenda Ye, M.D.
<b>Statistical Review</b>	Satish Misra, Ph.D. DBV
<b>Pharmacology Toxicology Review</b>	Ronald Honchel, Ph.D.
<b>OPQ Review</b>	Anne Marie Russell, Ph.D. Martin Haber, Ph.D. Li Hsieh, Ph.D. Thuy Nguyen, Ph.D. Assadollah Noory, Ph.D. Fang Wu, Ph.D.
<b>Microbiology Review</b>	Jessica G. Cole, Ph.D.
<b>Clinical Pharmacology Review</b>	Christy S. John, Ph.D.
<b>CDTL Review</b>	Nushin Todd, M.D.
<b>OSE/DMEPA</b>	Leeza Rahimi, Pharm.D.
<b>OPDP</b>	Adam George, Pharm.D.
<b>Pediatric Review</b>	Mona Khurana, M.D. Carrie Ceresa
<b>Labeling Team</b>	Ann Marie Trentacosti, M.D. Jeanine Best, MSN, RN, PNP
<b>Project Manager</b>	Frank Lutterodt (project manager)
<b>Division Director</b>	Libero Marzella, M.D.

OND=Office of New Drugs; OPQ=Office of Pharmaceutical Quality; CDTL=Cross-Discipline Team Leader; OSE=Office of Surveillance and Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis

## Overview

Barium sulfate has been marketed as unapproved drug products for many years for use in x-ray and CT examinations to help better delineate the gastrointestinal tract. NDA #208036 contains the safety and efficacy data to support this and subsequent applications for barium sulfate containing products (b) (4). Bracco Diagnostics is the sponsor and has marketed barium sulfate products since 2008 when they purchased the product line from E-Z-EM. Bracco is apparently the sole source of barium products in the United States. (b) (4)

(b) (4)

Readi-Cat 2 is to be used for computed tomography (CT) of the abdomen (b) (4)

The application is recommended for approval by the division director and the CDTL. After reviewing the information in the reviews, I concur with the recommendation. The review staff did an excellent job in summarizing and resolving issues related to this application and derived a label that is consistent with the data at hand. There was an emphasis on relating the current drug product relative to products that have been historically marketed. This allowed the clinical staff to depend on studies from the medical literature in which comparable products to this product were studied. This supported the clinical utility of the drug. Controls have been established for manufacturing that will identify and limit trace elements and other impurities that could prove more harmful than the barium sulfate if not adequately controlled. (b) (4)

(b) (4) This is the second barium sulfate NDA and it is for a product to be used in visualization of the gastrointestinal tract during CAT scan procedures.

(b) (4)

**Section 1: Benefit-Risk Framework (BRF)**

**1. Benefit-Risk Assessment**

The benefit risk assessment for Read-Cat 2 and Read-Cat 2 Smoothie supports that the application be approved for computed tomography (CT) of the abdomen (b) (4). The low density and low viscosity of the product allows for adequate visualization of the gastrointestinal tract in CT testing. The efficacy and safety is supported by reports from the medical literature using products of comparable attributes. Because the barium sulfate is mined and possibly coexists with trace elements and heavy metals that may pose potential toxic effects, the development and incorporation of manufacturing controls, testing and specifications allow for the production of a safe product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>• Read-Cat 2 contains barium sulfate in (b) (4) average particle sizes to be used for computed tomography (CT) of the abdomen (b) (4)</li> <li>• Barium sulfate has been marketed for many years as an unapproved drug product.</li> <li>• Barium is an alkaline earth metal that has a high chemical reactivity and is never found in nature as a free element. It is biologically inert whose mechanism of action as a radio contrast drug is to attenuate x-rays and allow visualization of the bowel.</li> <li>• There is low systemic absorption of barium and most is eliminated through the gastrointestinal tract.</li> <li>• Barium products differ in their concentration, viscosity and density depending on their use and route of administration.</li> <li>• This application references the safety and efficacy data submitted in NDA# 208036.</li> </ul>	<ul style="list-style-type: none"> <li>• Because of the long marketing history, the application depends on published studies to support the efficacy of the product and adverse event reporting to support the safety</li> <li>• The applicant was permitted to submit published literature. The chemists compared the current product to the historically marketed products to create a bridge between the products likely used in the clinical trials with the current product(s).</li> <li>• This is the second (b) (4) barium products to be submitted.</li> <li>• (b) (4) serves as the source of barium.</li> <li>• Read-Cat 2 is manufactured, packaged and labeled at E-Z-EM in Quebec, Canada..</li> <li>• The barium ingredient in this product will be the same for all of the applications although there will be differences in particle size, density and viscosity.</li> <li>• The Read-Cat 2 barium products marketed from 1985 to 2015 are similar in formulation, particle size and viscosity from the quality standpoint and are expected to have similar clinical characteristics.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Diagnostic Options	<ul style="list-style-type: none"> <li>• Barium Sulfate suspensions of 1 to 2% are generally used to fill the bowel lumen and not to coat the mucosa.</li> <li>• 2 – 3% solutions of Iodinated water-soluble contrast</li> <li>• Endoscopy, colonoscopy, sonography, magnetic resonance imaging, and CAT (computerized axial tomography) with or without contrast.</li> </ul>	<ul style="list-style-type: none"> <li>• Iodinated contrast agents are preferred to barium suspensions when there is a risk of bowel leak or obstruction.</li> <li>• Read-i-Cat 2 will be labeled not to be used when there is evidence of possible perforation or obstruction.</li> <li>• Read-i-Cat 2 is a low density, low viscosity product that allows for the proper flow properties to fill the gastrointestinal tract to assist in the location of normal bowel structures.</li> </ul>
Benefit	<ul style="list-style-type: none"> <li>• Barium is used in CT scans to differentiate the bowel from other organs in the abdomen.</li> <li>• Forty-eight of 151 publications were reviewed to support the efficacy of barium.</li> </ul>	<ul style="list-style-type: none"> <li>• The focus of the review was to verify the utility of the various barium sulfate products for enhancing the visualization of the various regions of the gastrointestinal tract. FDA did not have access to patient level data so verification of the quantitative performance of barium could not be conducted. This will limit the indication to a structural delineation.</li> <li>• The review supported the comparability of the proposed commercial product to the historical unapproved barium Read-i-Cat 2 products.</li> <li>• The medical literature included studies utilizing barium sulfate to visualize various sections of the gastrointestinal tract by different routes of administration (depending on the area to be visualized, e.g. rectal administration for colon).</li> <li>• There were no studies submitted that used Read-i-Cat 2. Four studies used E-Z-Cat Dry (1 – 1.7%) which the reviewer accepted similar enough to Read-i-Cat 2 with regard to barium concentration to support the efficacy of Read-i-Cat 2. There was no evidence of sedimentation and the studies demonstrated the efficacy of dilute barium to opacify the gastrointestinal tract in CT imaging of the abdomen and pelvis.</li> </ul>
Risk	<ul style="list-style-type: none"> <li>• The typical non-clinical data are not provided.</li> <li>• 99.99% of the dose is not absorbed.</li> <li>• The sponsor submitted their safety database for the time period between 1/1/2009 to 7/31/2014. (NDA # 208036)</li> <li>• Historical records of spontaneous reports from 7/1/1997 to</li> </ul>	<ul style="list-style-type: none"> <li>• Barium sulfate is inert and not absorbed by the gastrointestinal tract. After oral administration, 0.16 – 0.26 x 10<sup>-6</sup> of ingested dose was excreted in the urine.</li> <li>• QT studies were not conducted and are not necessary because barium sulfate is inert and not absorbed systemically to a significant degree.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>12/31/2007 were provided. (NDA # 208036)</p> <ul style="list-style-type: none"> <li>Scientific reports and practice guidelines were a source of safety data.</li> <li>(b) (4)</li> <li>The presence of trace elements from the (b) (4) represents a risk to the patient. To assess this risk, the sponsor conducted studies to evaluate the content of 55 trace elements in the (b) (4). Potential impurities included (b) (4).</li> <li>(b) (4) may be present in some drug substance lots.</li> </ul>	<ul style="list-style-type: none"> <li>Because the product is biologically inert, has limited systemic absorption, is eliminated primarily in the feces and has a long history of use, non-clinical studies are not necessary. The drug product should not be used in pregnant women (radiation exposure to the fetus) so reproductive-toxicology studies are not needed.</li> <li>Populations of patients at risk for adverse events are provided by historical use.</li> <li>Serious adverse events related to barium sulfate occur as a result of aspiration, impaction and leakage in gastrointestinal perforations.</li> <li>The source of the ore is controlled.</li> <li>(b) (4) are controlled at the (b) (4) level.</li> <li>Trace elements are measured in batches and specifications for admissible levels have been established. An expert opinion report provided by the sponsor provided estimates of acceptable limits. FDA believes the impurity limits are acceptable.</li> <li>The sponsor agreed to include a USP heavy metals screening test (b) (4) specification. If the screening test is positive, the sponsor will add sensitive tests for (b) (4).</li> <li>Readi-Cat 2 contains sorbitol which may cause a laxative effect.</li> <li>Approximately (b) (4) doses have been administered yearly between 1985 and 2015.</li> </ul>
<p>Risk Management</p>	<ul style="list-style-type: none"> <li>The labeling warns of conditions in which barium sulfate should not be administered to a patient.</li> <li>There is limited pediatric use data available with regard to dosing.</li> </ul>	<ul style="list-style-type: none"> <li>The drug substance and final product quality will be ensured by the manufacturing process and controls in order to yield consistent batches.</li> <li>Survey data was insufficient to identify a dose for pediatric patients.</li> <li>The survey data did suggest that Readi-Cat 2 may be used across all pediatric age groups.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		<ul style="list-style-type: none"><li>• The pediatric dose of Readi-Cat 2 for patients &lt; 12 years of age recommends that the dose be adjusted based on relative GI volume.</li></ul>

## 2. Further discussion to support regulatory action

### Product Quality

The sponsor made a commitment to perform methods validation of the Inductively Coupled Plasma (ICP) method to be used in conjunction with USP heavy metal screening of barium sulfate (b) (4) to provide validation data, along with justification of any revised heavy metal specifications by supplement, post approval of the NDA.

### Nonclinical Pharmacology/Toxicology

The pharmacology-toxicology review staff could not make a recommendation based on non-clinical data given that there is limited data provided. They did not raise significant concerns, however, because the product is for the most part not absorbed systemically and for many people it will be a once in a life-time dose. It should not be used in pregnant women so there is no need for reproductive toxicology data.

### Advisory Committee Meeting

No advisory committee meeting was held to review this application.

### Pediatrics

The sponsor conducted a survey among product users in lieu of submitting an initial Pediatric Study Plan (iPSP) because there is very little data in the literature regarding barium use in pediatric patients. The General Barium Survey (targeted radiologists, technicians, managers) was conducted but poor participation (19%) limits the generalizability of the information obtained. The survey results suggest that REDI-CAT 2 is used across all pediatric age groups. The safety and efficacy of barium sulfate can be extrapolated from adults to pediatric patients.

REDI-CAT has been available for years and the dosing for children < 12 years of age varies with each center conducting the studies. There is limited data in the literature to support a specific dose for children < 12 years of age. Recognizing the current marketing of REDI-CAT 2 and use in pediatric patients, for this product the dosing instruction will simply convey that the dose should be adjusted based on relative GI volume. Relative GI volume may be calculated at different institutions based on weight, total body surface area or other factors. We have intentionally not included any these factors but if we obtain more information in the future we may adjust the labeling.

### Risk Evaluation and Mitigation Strategies (REMS)

There are no REMS.

### Postmarketing Requirements and Commitments

The sponsor will use the USP method to screen (b) (4) for heavy metals (such as (b) (4) (b) (4)). If the USP test exceeds (b) (4) ppm, then the sponsor will conduct the Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method. They will validate the test method and provide data from the validation studies with revised specifications.

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CHARLES J GANLEY  
01/15/2016