CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208143Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review	
NDA/SDN	NDA 208143 / SDN 1 \\CDSESUB1\evsprod\NDA208143\
Type/Category	Original-1 (Unknown)
Brand Name	Barium Sulfate powder for suspension 2% w/v
Generic Name	READI-CAT 2; READI CAT 2 SMOOTHIE
Receipt Date	December 18, 2014
PDUFA Date	October 16, 2015
Proposed Indication	READI-CAT 2 and READI-CAT 2 SMOOTHIE products are indicated for use in Computed Tomography of the abdome (b) (4)
Dosage Form	READI-CAT 2 and READI CAT 2 SMOOTHIE is a barium sulfate powder for suspension (2% w/v) for oral administration
Route of Administration	Oral
Dosing Regimen and Strength	The typical adult dose can range from 450 – 900 mL
Applicant	Bracco Diagnostics, Inc.
OND Division	Division of Medical Imaging Products (DMIP)
OCP Divisions	Division of Clinical Pharmacology V (DCPV)
OCP Reviewers	Christy S John, Ph.D.
OCP Team Leaders	Gene Williams, Ph.D.

Table of Contents

1 EXECUTIVE SUMMARY

The Applicant has submitted a 505(b)(2) application for the approval of READI-CAT 2 and READI-CAT 2 SMOOTHIE products for use in Computed Tomography of the abdomen (b)(4) [redacted]. No clinical or clinical pharmacology studies were performed by the applicant. The dosing, safety and efficacy data for the approval of this application is based upon Guidelines and appropriateness criteria issued by the American College of Radiology (ACR); Radiology textbooks; and published papers and review articles retrieved from the literature. The proposed adult dose is 450-900 mL depending on the patient's clinical condition and the section of the gastrointestinal tract to be viewed. Barium sulfate is an insoluble compound and is biologically inert. The systemic absorption of barium sulfate is extremely limited; it is not metabolized and is eliminated unchanged in the feces.

1.1 RECOMMENDATIONS

The NDA 208-143 is acceptable from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding the labeling language.

1.2 POST-MARKETING REQUIREMENTS AND COMMITMENTS

None.

Signatures:

Reviewer: Christy S John, Ph.D. Division of Clinical Pharmacology V	Team Leader: Gene Williams, Ph.D. Division of Clinical Pharmacology V

Cc: DMIP: RPM – F Lutterodt; MO – B Ye; MTL –A Gorovets
DCPV: DDD – B Booth; DD Nam A Rahman

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The Applicant has submitted a 505(b)(2) application for the approval READI-CAT 2 and READI-CAT 2 SMOOTHIE products for use in Computed Tomography of the abdomen (b) (4)

No clinical or clinical pharmacology studies were conducted by the applicant. Barium Sulfate medical imaging products have been used since the early 1900s as radiopaque contrast agents to opacify the GI tract following oral administration (pharynx, hypopharynx, esophagus, stomach, duodenum, and small bowel exams) or rectal administration (colon and distal segments of the small bowel). The dosing, safety and efficacy data for the approval of this application is based upon Guidelines and appropriateness criteria 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; and published papers and review articles retrieved from the literature and post-marketing surveillance (PMS) database based on an estimated exposure of more than (b) (4) patients worldwide, in the period comprised between January 1, 2009 to July 31, 2014.

READI-CAT 2 and READI-CAT 2 SMOOTHIE products are for oral use and contain 2% w/v of barium sulfate. The recommended dose is 450-900 mL depending on the patient's clinical condition and the section of the gastrointestinal tract to be viewed.

The time for barium sulfate to produce adequate opacification of a GI segment varies according to the route of administration, the concentration, and the viscosity of the administered barium suspension. Maximum opacification of the esophagus, stomach, and duodenum occurs almost immediately after the oral administration of the barium sulfate suspension whereas opacification of the small bowel occurs between 15 and 90 minutes after oral administration of the barium sulfate suspension, Timing of opacification of the colon following rectal administration of the barium suspension (barium enema) depends on a number of factors such as positioning of the patient during the procedure, hydrostatic pressure, and rate of administration.

Barium sulfate is an insoluble compound and is biologically inert. The systemic absorption of barium sulfate is extremely limited; it is not metabolized and is eliminated unchanged in the feces. After oral ingestion of a barium sulfate preparation, $0.16\text{-}0.26 \times 10^{-6}$ of the ingested dose was subsequently excreted via the urinary tract whereas urinary excretion of rectally administered. Barium sulfate was in the range of $0.02\text{-}0.09 \times 10^{-6}$ of the administered dose. The clinical significance of absorption of such small amounts is speculative; particularly in view of the presence of spectrometrically measurable trace amounts of barium in many water supplies.

2 QUESTION-BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

A listing of the ingredients for each of the formulations is provided in **Table 1**.

Table 1. Readi-Cat 2 and Readi-Cat 2 Smoothie formulations

Component Name	Function	Composition % w/v				
		Readi-Cat 2	Readi-Cat 2 Smoothies			
			Banana	Creamy Vanilla	Berry	Mochaccino
						(b) (4)
Barium sulfate (b) (4)	Drug Substance	2.0898	2.0898	2.0898	2.0898	2.0898
Xanthan Gum						(b) (4)
Simethicone Emulsion						
Potassium Sorbate						
Sodium Benzoate						
Benzoic Acid						
Citric Acid (b) (4)						
Sodium Citrate						
Sorbitol Solution						
Purified Water						
Saccharin Sodium						
Artificial Vanilla Flavor						
(b) (4)						
Naturally (b) (4) Banana Flavor						
Natural and Artificial Orange Flavor						
Natural and Artificial Blueberry Flavor						
Natural and Artificial (b) (4) Chocolate Flavor						
Natural and Artificial Coffee (b) (4) Flavor						

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Barium sulfate's use as a contrast agent is based on the high atomic number of barium which enhances the absorption of X-ray beams and allows opacification of the GI tract during conventional X-ray and computed tomography (CT) examinations. Barium sulfate is a heavy metal characterized by a high atomic number (Z=56) and a K shell binding energy (K-edge) of 37.4 keV which is close to the mean energy of most diagnostic X-ray beams and therefore ideal for absorption of X-rays. Although iodinated water soluble agents have similar characteristics (iodine atomic number and K-edge are 53 and 33.2 keV, respectively), barium sulfate products remain the preferred agents for imaging the GI tract because of greater delineation of mucosal details and resistance to dilution.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

READI-CAT 2 and READI-CAT 2 SMOOTHIE products are barium sulfate suspensions 2.0% (w/v) for oral administration. The proposed adult dose is 450-900 mL depending on the patient's clinical condition and the section of the gastrointestinal tract to be viewed.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The safety, efficacy and dosing data for the approval of this application is based upon Guidelines and appropriateness criteria 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; and published papers and review articles retrieved from the literature and post-marketing surveillance (PMS) database based on an estimated exposure of more than (b) (4) patients worldwide in the period between January 1, 2009 to July 31, 2014. There is no dose-response relationship described in the literature.

The time for barium sulfate to produce adequate opacification of a GI segment varies according to the route of administration, the concentration, and the viscosity of the administered barium suspension. Maximum opacification of the esophagus, stomach, and duodenum occurs almost immediately after the oral administration of the barium sulfate suspension whereas opacification of the small bowel occurs between 15 and 90 minutes after oral administration of the barium sulfate suspension, Timing of opacification of the colon following rectal administration of the barium suspension (barium enema) depends on a number of factors such as positioning of the patient during the procedure, hydrostatic pressure, and rate of administration.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No QT study of the type recommended in FDA Guidance has been performed. Transient ECG changes are known to occur during visceral stimulation and have been reported in association with gastroscopy and sigmoidoscopy. ECG abnormalities are more frequent in elderly patients with clinical history of cardiac disease; patient dehydration, a condition of stress and anxiety during the examination, and the concomitant administration of antispasmodic drugs may represent contributing factors to the development of arrhythmias during barium enema or enteroclysis.

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?

There is no unresolved dose or dosing regimen issues.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single dose and multiple dose PK parameters?

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

2.2.5.3 What are the characteristics of drug absorption?

2.2.5.4 What are the characteristics of drug distribution?

Barium sulfate is an insoluble compound and is biologically inert. The systemic absorption of barium sulfate is extremely limited (see 2.2.5.7, below).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

2.2.5.6 What are the characteristics of drug metabolism?

2.2.5.7 What are the characteristics of drug excretion?

Atomic absorption spectrometry has been used to measure urinary excretion of barium after oral and rectal administration of Barium Sulfate suspensions. After oral ingestion of a Barium Sulfate preparation, $0.16\text{-}0.26 \times 10^{-6}$ of the ingested dose was excreted via the urinary tract whereas urinary excretion of rectally administered. Barium sulfate was in the range of $0.02\text{-}0.09 \times 10^{-6}$ of the administered dose. By subtraction, greater than 99.99% of the dose is not absorbed. The clinical significance of absorption of such small amounts is speculative

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

2.2.5.9 How do the PK parameters change with time following chronic dosing?

2.2.5.10 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?

There are no PK studies reported as barium sulfate is insoluble and is not systemically absorbed.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

No dosage regimen adjustments are recommended for specific patient populations.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or dose-response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions?

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug an inhibitor and/or an inducer of transporters?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 What other co-medications are likely to be administered to the target population?

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Barium sulfate is not absorbed. Further, barium sulfate is biologically inert. For both of these reasons, CYP and transporter related interactions are not expected. There are no known interactions with other medicinal products.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food will not render barium sulfate soluble. The label is silent on the effect of food as well as pre-dose patient preparation (i.e., fasting prior to dosing). There is literature on the use of BaSO4 taken with food for evaluation of gastric motility, however, this is not an indication proposed by the applicant.

2.5.4 When would a fed BE study be appropriate and was one conducted?

2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured is free, bound or total measured?

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification?

2.6.4.3 What are the accuracy, precision and selectivity at these limits?

2.6.4.4 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler).

There are no analytical methods reported in literature for the determination of barium sulfate in any clinical studies reported by the applicant.

3 DETAILED LABELING RECOMMENDATIONS

Review of the package insert has yet to be finalized. See Appendix 1 for the applicant's proposed package insert.

APPENDIX 4.1 APPLICANT'S PROPOSED PACKAGE INSERT

6 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/

CHRISTY S JOHN
08/12/2015

GENE M WILLIAMS
08/12/2015
I concur with the recommendations

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**208-143**	**Brand Name**	Barium sulfate 2% suspension
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	READI-CAT® 2 READI-CAT® 2 Smoothie
Medical Division	**DMIP**	**Drug Class**	**Diagnostic**
OCP Reviewer	**Christy S John, Ph.D.**	**Indication(s)**	READI-CAT® 2 READI-CAT® 2 SMOOTHIE products are indicated for use in Computed Tomography of the abdomen (b) (4) [redacted]
OCP Team Leader	**Gene Williams, Ph.D.**	**Dosage Form**	READI-CAT® 2 READI-CAT® 2 SMOOTHIE products are barium sulfate suspensions 2.0% (w/v) for oral administration.
Pharmacometrics Reviewer		**Dosing Regimen**	The typical adult dose can range from 450 – 900 mL of READI-CAT 2. It is Intended for a single use.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Date of Submission	**December 18, 2014**	**Route of Administration**	**Oral suspension**
Estimated Due Date of OCP Review	**August 10, 2015**	**Sponsor**	**Bracco Diagnostics Inc.**
Medical Division Due Date	**August 16, 2015**	**Priority Classification**	**1S**
PDUFA Due Date	**October 18, 2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Literature References	**X**	**7**		This is a 505(b)(2) application for barium sulfate oral suspension. There are no clinical pharmacology studies conducted by the sponsor. The sponsor has submitted literature references in support of the package insert.
Total Number of Studies		**7**		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?			X	
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?			X	
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?			X	
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?			X	
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?			X	

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____X____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Christy S. John, Ph.D.

Reviewing Clinical Pharmacologist Date

Gene Williams, Ph.D.

Team Leader/Supervisor Date

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

/s/

CHRISTY S JOHN
02/10/2015

GENE M WILLIAMS
02/10/2015
I concur with the recommendations.