

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208844Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208-844	SDN	1
Applicant	Bracco Diagnostics, Inc.	Submission Date	12/14/2015
Generic Name	Barium sulfate paste (b) (4) % (w/v) for oral administration	Brand Name	VARIBAR PUDDING
Drug Class	Imaging		
Indication	VARIBAR <i>PUDDING</i> is a radiopaque contrast media indicated for use in adult and pediatric patients for modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology.		
Dosage Regimen	The typical dose is 5 mL in adults (b) (4) patients. During a single modified barium swallow examination, multiple doses of VARIBAR <i>PUDDING</i> may be administered.		
Dosage Form	Paste	Route of Administration	Oral
OCP Division	DMIP	OND Division	DCP V
OCP Review Team	Primary Reviewer(s)		Secondary Reviewer/ Team Leader
Division	Christy S John, Ph.D.		Gene Williams, Ph.D.
Pharmacometrics	N/A		N/A
Genomics	N/A		N/A
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	February 12, 2016	74-Day Letter Date	2/26/2016
Review Due Date	August 19, 2016	PDUFA Goal Date	October 14, 2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
<input checked="" type="checkbox"/> Yes			
<input type="checkbox"/> No			
If no list reason(s): The application is 505 (b) (2) and relies on literature information. There are no new data or analyses of clinical or non-clinical data; the application relies on literature and analyses submitted in the applicant's prior NDAs (NDAs 208-143 and 208-036, both of which were approved). The lack of new data and analyses is consistent with negotiations between the applicant and the FDA that occurred under IND 115,090 and that took place prior to submission of the fore-mentioned NDAs. The preliminary meeting minutes that capture the agreement were finalized November 25, 2013.			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			
Is there a need for clinical trial(s) inspection?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			

If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Clinical Pharmacology Summary
Bioanalytical and Analytical Methods		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Labeling
			<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
<input type="checkbox"/> Metabolism Characterization			
<input type="checkbox"/> Transporter Characterization			
<input type="checkbox"/> Distribution			
<input type="checkbox"/> Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
<input type="checkbox"/> Absolute Bioavailability			
<input type="checkbox"/> Relative Bioavailability			
<input type="checkbox"/> Bioequivalence			
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
Human Pharmacokinetics			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
Intrinsic Factors			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			

<input type="checkbox"/> Effects of Primary Drug				
Pharmacodynamics				
<input type="checkbox"/> Healthy Subjects				
<input type="checkbox"/> Patients				
Pharmacokinetics/Pharmacodynamics				
<input type="checkbox"/> Healthy Subjects				
<input type="checkbox"/> Patients				
<input type="checkbox"/> QT				
Pharmacometrics				
<input type="checkbox"/> Population Pharmacokinetics				
<input type="checkbox"/> Exposure-Efficacy				
<input type="checkbox"/> Exposure-Safety				
Total Number of Studies	In Vitro	0	In Vivo	0
Total Number of Studies to be Reviewed		0		0

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
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)?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
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?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code,	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	The application is 505 (b) (2) and relies on literature information. There are no new data or analyses

<p>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?</p>		<p>of clinical or non-clinical data; the application relies on literature and analyses submitted in the applicant’s prior NDAs (NDAs 208-143 and 208-036, both of which were approved). The lack of new data and analyses is consistent with negotiations between the applicant and the FDA that occurred under IND 115090 and that took place prior to submission of the fore-mentioned NDAs. The preliminary meeting minutes that capture the agreement were finalized November 25, 2013.</p>
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Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist

Data

<p>1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A</p>	<p>The application is 505 (b) (2) and relies on literature information. There are no new data or analyses of clinical or non-clinical data; the application relies on literature and analyses submitted in the applicant’s prior NDAs (NDAs 208-143 and 208-036, both of which were approved). The lack of new data and analyses is consistent with negotiations between the applicant and the FDA that occurred under IND 115090 and that took place prior to submission of the fore-mentioned NDAs. The preliminary meeting minutes that capture the agreement were finalized November 25, 2013.</p>
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<p>2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A</p>	
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Studies and Analysis

<p>3. Is the appropriate pharmacokinetic information submitted?</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>	
<p>4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>	

(i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
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?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

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
03/02/2016

GENE M WILLIAMS
03/02/2016

I concur with the recommendation