CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208844Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: APPROVAL, pending final labeling.

NDA 208844
Quality Review #1

APPLICATION INFORMATION	
Drug Name/Dosage Form	Varibar Pudding (barium sulfate) paste
Strength	40% w/v
Route of Administration	Oral
Rx/OTC Dispensed	Rx (505b2)
Applicant	Bracco Diagnostics Inc 259 Prospect Plains Rd Building H Monroe Township, NJ 08831
US agent, if applicable	Not applicable

SUBMISSION(S) REVIEWED		
EDR SEQUENCE #	**DATE**	**DISCIPLINE(S) AFFECTED**
0000	14-Dec-2015	NDA submission
0003	19-Feb-2016	Quality - Cross reference to N208036 supplement for drug substance
0005	20-Jul-2016	Quality – revise assay acceptance criteria and strength

QUALITY REVIEW TEAM		
DISCIPLINE	**REVIEWER**	**BRANCH/DIVISION**
Drug Substance	Anne Marie Russell, Ph.D.	Branch VI/Division II/ONDP/OPQ
Drug Product		
Process		
Microbiology	Jessica Cole, Ph.D.	Microbiology/OPF/OPQ
Facility	Brian (BJ) Ryan	OPF/OPQ
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	N/A	N/A
Application Technical Lead	Anne Marie Russell, Ph.D.	Branch VI, Division II, ONDP
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Analysis	N/A	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF	TYPE	HOLDER	ITEM	STATUS	REVIEWER
(b) (4)	Type III		(b) (4)	N/A	Sufficient information provided in NDA.
	Type IV			Adequate	A.M. Russell, Ph.D. 03-Nov-2015 See review in DARRTS

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION	DESCRIPTION
Aug 2012, Nov 2013, Oct 2014	PIND 115090	Meeting minutes
Drug Substance (M3.2.S), Nonclinical (M4) and Clinical (M5) information is cross referenced to NDA 208036	N208036 [E-Z-HD (barium sulfate) powder for suspension], submitted on December 11, 2014	Original (b) (4) NDA

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	none			
Pharmacology/Toxicology	none			
CDRH	none			
Clinical	pending			Brenda Ye, MD
Other	none			

Table of Contents

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for approval. Labeling comments will be finalized during the multi-disciplinary review managed by OND.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable None.

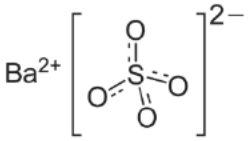
II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	This is an original new drug application for a radiopaque contrast media, VARIBAR pudding (barium sulfate) paste for oral administration, submitted as a 505(b)(2) application without clinical data, for use in adults and pediatric patients for modified barium swallow examinations.
Duration of Treatment	As needed.
Maximum Daily Dose	The typical dose is 5 mL in adults (b) (4) patients. During a single modified barium swallow examination, multiple doses of VARIBAR PUDDING may be administered
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance:
Chemical Name and Structure:
Barium sulfate $BaSO_4$ (molecular weight 233.4 g/mol)



The drug substance, barium sulfate, (b) (4) The drug

substance is cross referenced to Bracco's NDA 208036, which was approved in January 2016.

Drug Product:
The drug product, VARIBAR® PUDDING, is a barium sulfate paste (40% w/v) for oral administration. It is a smooth, off-white to lightly colored, preservative containing paste with pudding like consistency and vanilla aroma. It is presented as a multi-dose/multi-patient use 230 mL fill in a white polyethylene tube with a (b) (4) screw cap.

In keeping with recently approved Bracco barium sulfate products (N208036, N208143), the proposed commercial product, Varibar pudding, has been sold in the US and used in clinical practice as an unapproved product for years. Since market introduction in 2000, it has been manufactured under the (b) (4) specifications, formulation, manufacturer and process. Thus there is considerable history for existing quality of the comparable product, which serves as the basis for the clinical determination of safety and efficacy, along with published literature.

Stability data were provided to support the proposed 24 month shelf life and 21 day in-use period at 25°C.

Facilities: Review by Brian J. Ryan finds the facilities acceptable, see next section.

Microbiology: Review by Jessica Cole, Ph.D. recommends for approval, see next section.

C. Special Product Quality Labeling Recommendations (NDA only) - none

D. **Final Risk Assessment**: see Attachment I at end of review

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER III: Environmental Analysis See Drug Product

CHAPTER IV: Labeling

R Regional Information

1.14 Labeling

At this time, labeling and package insert language is not final. Labeling review, revisions and negotiations will be handled through the clinical team.

Immediate Container Label

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER V: Process See Drug Product
CHAPTER VI: Facilities See next section.
CHAPTER VII: Biopharmaceutics not needed.
CHAPTER VIII: Microbiology See next section.
CHAPTER IX: Additional Quality Discipline not needed

ATTACHMENT I: Final Risk Assessment: NDA Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Comparability of proposed commercial product with unapproved historical product.	Absence of "reference listed drug"	N/A	Comparison of quality with products sold since market introduction in 2000.	Acceptable	None.
Drug substance (identity, heavy metals, particle size)	See N208036 Integrated Quality Assessment in Panorama			Acceptable	Commitment for (b) (4)
Quality inactive ingredients	N/A	N/A	Quality met by USP, DMF and COAs	Acceptable	None

OVERALL ASSESSMENT AND SIGNATURES:

Primary Review: Anne Marie Russell, Ph.D., Application Technical Lead (ATL) and reviewer for all sections of the above document (Executive Summary, Drug Substance, Manufacturing Process, Drug Product, Labeling, Environmental Assessment):

Anne M. Russell -S
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Secondary Review: Danae Christodoulou, Ph.D., Branch Chief

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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208844	**Submission Type:NDA**	**Established/Proper Name: Barium Sulfate Paste**
Applicant: Bracco Diagnostics	**Letter Date:12/14/15**	**Dosage Form: Paste**
Chemical Type:	**Stamp Date:12/14/15**	**Strength: (b)(4)% (w/v)**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			Describe potential review issues here or on additional sheets

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☒	☐	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other_____	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

APPEARS THIS WAY ON ORIGINAL

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other_____		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	Assay, viscosity, preservatives
36.		Excipients	☒	☐	flavoring
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☐	Not specified
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☒	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Exclusion claimed
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Facilities and Equipment ○ Adventitious Agents Safety Evaluation ○ Novel Excipients ❑ Regional Information ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols				
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
	DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be	☐	☐	☒	

C. FILING CONSIDERATIONS					
	licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using	☒	☐	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☒	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	Literature references are in English
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☐	☒	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples				

Note: This NDA is the third product (b) (4) barium sulfate products marketed by Bracco (EZ-EM) as an unapproved product. The prior two NDAs for barium sulfate products have been approved in Jan 2016 – N208036 E-Z-HD (98% w/w barium sulfate powder for suspension) and N208143 Readi-Cat 2 (2% w/v barium sulfate suspension).

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

The drug product formulation is shown below in Table A

3.2.P.1 Description and Composition of Drug Product (VARIBAR® *PUDDING*, Barium Sulfate Paste)

3.2.P.1.1 Description of Dosage Form

VARIBAR® *PUDDING* is a barium sulfate paste ((b) (4)% w/v) for oral administration. It is a smooth, off-white to lightly colored paste with pudding like consistency and vanilla aroma.

VARIBAR *PUDDING* is presented as a multi-dose use 230 mL fill in a white polyethylene tube with a (b) (4) screw cap.

3.2.P.1.2 Drug Product Composition

The amount of each component (% w/v) per 230 mL fill size is presented Table A below.

Table A: Drug Product Composition

Component number	Component Name	Percent composition (% w/v)	Amount (g) per unit (230 mL)	Function	Grade
(b) (4)	Barium sulfate (b) (4)	40.0000[b]	92.000	Contrast agent	USP
	Sodium Benzoate			(b) (4)	USP/NF
	Potassium Sorbate				USP/NF
	Xylitol				USP/NF
	Citric Acid (b) (4)				USP
	Simethicone Emulsion (b) (4)				USP
	Polysorbate 80				USP/NF
	Glycerin				USP
	Xanthan Gum				USP/NF
	Carboxymethylcellulose Sodium				USP
	Maltodextrin				USP/NF
	Ethyl Vanillin				USP/NF
	Artificial Vanilla Flavor[a]				GRAS; 21CFR 172.5 compliant
	Saccharin Sodium				USP
	Purified Water				USP
					(b) (4)

Signed: Anne Marie Russell, Ph.D. Application Team Lead (OPQ/ONDP/DNDPIII/Branch VI)

Anne M. Russell -S

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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/

ANNE M RUSSELL
02/16/2016